MEDICARE COVERAGE FOR INVESTIGATIONAL DRUGS: EXPLORING THE OPTIONS

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Cheryl F. Austein, Elizabeth H. Hadley, Margaret Walkover

James Bell Associates
Health Technology Associates

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Legislative Mandate

Section 202(k)(1)(A) of the Medicare Catastrophic Coverage Act (MCCA) of 1988 required the Secretary to study "**the possibility of including drugs which have not yet been approved under Section 505 or 507 of the Federal Food, Drug, and Cosmetic Act and biological products which have not been licensed under Section 351 of the Public Health Service Act but which are commonly used in the treatment of cancer or in immunosuppressive therapy and other experimental drugs and biological products as covered outpatient drugs under the medicare program....**" Although the outpatient drug benefit contained in the MCCA has been repealed, the issues raised in this study remain relevant to other drug benefits currently available under Medicare.

Report Organization

The report consists of five major sections:

- Description and analysis of the characteristics of categories of investigational drugs used for treatment purposes;
- Description and analysis of Medicare coverage policies;
- Description of other third-party drug coverage policies;
- Analysis of options for Medicare coverage of investigational drugs, including economic implications of Medicare coverage of investigational drugs; and
- Conclusions.

Characteristics of Categories of Investigational Drugs Used for Treatment Purposes

FDA's drug approval process divides drugs into two very broad categories: drugs that are approved for marketing and therefore by definition have an approved New Drug Application (NDA); and drugs that have not been approved for marketing. In theory these unapproved drugs are distributed only in clinical trials pursuant to protocols contained in their investigational new drug applications (INDs).

Historically, however, there have emerged a number of terms to describe situations where FDA has authorized the use of unapproved drugs for treatment purposes outside of clinical trials, but still under the auspices of an IND. With the promulgation of the Treatment IND Regulations in May of 1987, FDA formalized the procedures under which it had been permitting the distribution of unapproved drugs for treatment purposes.

A comparison of Treatment IND drugs with other investigational drugs raises two questions with important implications for coverage policy:

1. Is the primary purpose of distributing the drug to obtain research data or to provide treatment?

2. Is there identical evidence of safety and effectiveness for all drugs that have been designated as Treatment INDs?

Medicare Coverage Policy for Drugs

In April 1987, as part of a lawsuit settlement in Federal District Court, HCFA published a description of its coverage decisionmaking process in the Federal Register. More recently, in January 1989, HCFA published a notice of proposed rulemaking (NPRM) to establish criteria and procedures for national coverage decisions. The proposed rule would establish the criteria for determining whether specific health care technologies could be considered "reasonable and necessary" and therefore covered under Medicare. The proposed rule constitutes HCFA's first attempt to establish in regulations its longstanding interpretation of the statutory terms "reasonable and necessary."

Under its proposal, HCFA would consider a service to be "reasonable and necessary" if it meets the following criteria:

- the service is safe and effective;
- the service is not experimental or investigational;
- the service is cost-effective;
- the service is appropriate.

Drugs and biologicals approved for marketing by FDA are considered safe and effective for Medicare purposes when used for indications specified in their labeling. In addition, FDA-approved drugs may be covered when used for indications other than those specified on their labeling as long as FDA or HCFA has not specified such use as non-approved. A drug

or biological product that has not obtained approval for marketing from FDA is considered experimental or investigational.

A review of the HCFA coverage policy raises several important issues regarding coverage of drugs:

1. Does HCFA cover drugs, devices and services in a consistent manner?

2. Does HCFA equate the use of all investigational drugs with research?

3. Why does Medicare cover treatment with Group C cancer drugs, which are provided to patients at no charge, and not Treatment IND drugs?

Other Government and Private Sector Policies on Investigational Drug Coverage

Several recent events have provided an opportunity for public comment and analysis of the issue of coverage for investigational drugs. In addition to Medicare, this issue is under consideration by other third-party payors, drug sponsors, providers and patients.

Discussion

In recent years FDA has accelerated the review process for drugs and biologicals for serious and life-threatening diseases and has permitted investigational drugs to be available for treatment prior to approval for marketing. At the same time, HCFA has proposed in regulation its criteria and procedures specifying health care technologies that could be considered "reasonable and necessary" and therefore covered under Medicare.

While the FDA has taken steps to make drugs more widely available prior to approval for marketing, HCFA will only cover items and services (with the exception of Group C cancer drugs) that have been proven safe and effective based on authoritative evidence, or that are generally accepted in the medical community as safe and effective for the condition for which they are used. HCFA does not cover drugs that FDA has permitted to be made available for treatment purposes but are still considered experimental. Because of this apparent discrepancy between FDA and HCFA policies, certain patients and providers, particularly those dealing with cancer and AIDS, are demanding a change to the Medicare coverage policy for investigational drugs.

Options

There are a series of options for the possibility of coverage of investigational drugs. The options range from maintaining current Medicare coverage policy, to expanding coverage to include all Treatment IND drugs; or in the alternative, to include selected investigational drugs, either on a drug-by-drug basis as a national coverage policy, or on a patient-by-patient basis at the discretion of local contractors. A fifth option is to eliminate coverage for Group C cancer drugs. Each option has relative strengths and weaknesses, and each could have some economic impact on Medicare.

Option One: Maintain the current Medicare drug coverage policy.

Option Two: Expand coverage to include all Treatment IND drugs.

Option Three: Expand coverage to include selected investigational drugs, on a drug-by-drug basis.

Option Four: Permit contractors to consider coverage for investigational drugs on a patient-by-patient basis.

Option Five: Eliminate coverage for Group C cancer drugs.

Conclusions

Based on an analysis of existing regulatory policy, experience to date with the use of investigational drugs for widespread treatment, and a review of the issues associated with insurance coverage for investigational therapies, it appears that:

- Treatment IND drugs represent a specific category of investigational drugs that FDA has designated for potentially widespread treatment use, within the guidelines of the Treatment IND protocol, but outside the clinical trials setting. Treatment IND drugs are a formal intermediate category between clinical investigation and marketing approval. No comparable designation exists for devices or for medical procedures.

- Of all the investigational drug categories designated by FDA, Treatment IND drugs and Group C drugs differ in several significant respects from investigational drugs

distributed in clinical trials. Medicare could modify its exclusive reliance for coverage on FDA marketing approval for drugs and defer to FDA's designation of Treatment IND drugs as it does for Group C cancer drugs.

- Expanded coverage by Medicare for selected investigational drugs would likely have limited immediate impact on expenditures, although coverage for investigational drugs could set a precedent for coverage of investigational devices and procedures.

CHAPTER ONE:
INTRODUCTION

LEGISLATIVE MANDATE

Section 202(k)(1)(A) of the Medicare Catastrophic Coverage Act (MCCA) of 1988 required the Secretary to study **"the possibility of including drugs which have not yet been approved under Section 505 or 507 of the Federal Food, Drug, and Cosmetic Act and biological products which have not been licensed under Section 351 of the Public Health Service Act but which are commonly used in the treatment of cancer or in immunosuppressive therapy and other experimental drugs and biological products as covered outpatient drugs under the medicare program...."** Although the outpatient drug benefit contained in the MCCA has been repealed, the issues raised in this study remain relevant to other drug benefits currently available under Medicare. [1]

The study was supported by the Office of the Assistant Secretary for Planning and Evaluation in consultation with an Advisory Board of consumers, experts in the fields of cancer chemotherapy and immunosuppressive therapy, representatives of pharmaceutical manufacturers, and other individuals, as mandated by the law. A list of the Advisory Board members appears in Appendix B. In addition, the study was assisted by an intradepartmental workgroup with representatives from the Public Health Service and the Health Care Financing Administration. (Appendix C)

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[1]Under Medicare Part A, drugs and biologicals may be covered if they are furnished by hospitals or skilled nursing facilities or as part of a hospice program. Under Part B, certain drugs and biologicals that cannot be self-administered may be covered as an integral part of a physician's services. Examples of other covered outpatient uses may include drugs and biologicals furnished by a hospital to outpatients, bloodclotting factors for use by hemophiliacs who do not require medical supervision, and certain immunosuppressives. In general, however, Medicare does not cover outpatient prescription drugs.

BACKGROUND

On July 1, 1988 Congress enacted the Medicare Catastrophic Coverage Act of 1988 (P.L. 100-360). This law made a number of significant changes to the Medicare program, including the establishment of a new catastrophic outpatient drug benefit under the Supplemental Medical Insurance (Part B) portion of the Medicare program. Specifically, section 1861(t)(3)(b) of the Social Security Act (the Act), as amended by section 202(a)(2)(C) of P.L. 100-360, provided for coverage of drugs used in immunosuppressive therapy and intravenous (IV) drugs administered in the home, effective January 1, 1990, and for coverage of other outpatient prescription drugs, biologicals and insulin, effective January 1, 1991. "Covered outpatient prescription drugs" for purposes of the law included:

- drugs that may be dispensed only upon prescription and that are approved for safety and effectiveness as a prescription drug under the Federal Food, Drug, and Cosmetic Act (FFDCA);
- biological products that may be dispensed only upon prescription and that are licensed under the Public Health Service Act; and
- insulin certified under the FFDCA.

On December 13, 1989, Congress repealed most of the Part A and Part B provisions contained in P.L. 100-360. However, the issues presented in this study as mandated by that law remain relevant, notwithstanding the fact that Medicare will no longer expand its program to encompass a new outpatient prescription drug benefit. Drugs and biologicals remain a covered benefit under the following conditions:

- for use in the hospital, which are ordinarily furnished by the hospital for the care and treatment of inpatients.
- furnished as incident to physicians' services, if they are of the type that cannot be self-administered.

The types of drugs discussed in this study may be administered in the hospital or by a physician, as well as on an outpatient, self-administered basis. Whether or not to cover investigational or experimental drugs, therefore, remains an issue under Medicare's current policies.

PURPOSE

The purpose of this study is to examine the implications of potential Medicare coverage for investigational drugs. The study explores the relationship between Medicare coverage and the regulation of therapeutic uses of investigational drugs, and assesses:

- whether all investigational categories of drugs are equivalent, or whether some have sufficient safety and effectiveness evidence to be made available for treatment purposes in broader patient populations.

- to what extent HCFA coverage policies could allow for coverage of selected investigational drugs that meet requirements for safety and efficacy and are appropriate to individuals' medical needs.

- the impact coverage for selected investigational drugs might have on Medicare expenditures.

- the policies developed by other third-party payers for covering investigational drugs.

The study parameters are limited to the MCCA mandate, and do not include extensive analysis of other issues that may be related to this discussion such as third-party payment

for research, coverage of off-label uses of drugs, and reimbursement for care associated with the use of investigational therapies.

REPORT ORGANIZATION

The report consists of five major sections:

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CHAPTER TWO:
CHARACTERISTICS OF CATEGORIES OF
INVESTIGATIONAL DRUGS USED FOR TREATMENT PURPOSES

This chapter presents an overview of FDA's regulation of investigational drugs. The chapter also highlights the categories of investigational drugs available for treatment use.

BACKGROUND

Investigational drugs are new drugs that have not yet been approved for marketing by FDA and that are the subject of clinical investigations.[2] Their status needs to be understood within the context of FDA's approval process for new drugs.

Before marketing a new drug, the manufacturer must obtain FDA approval of a new drug application (NDA).[3] To submit an NDA, the manufacturer needs first to have conducted pre-clinical (animal) tests and clinical trials of the drug in humans to demonstrate that it is safe and effective under the criteria specified in section 505(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Ordinarily the manufacturer needs to ship the drug in interstate commerce in order to complete these tests. However, section 505(a) of the Act

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[2] 21 U.S.C. section 355(i); Federal Food, Drug, and Cosmetic Act, ("FFDCA") section 505(i). 21 C.F.R. section 312.3(b). A drug that has already been approved for marketing is considered an investigational drug is it is the subject of a formal study to determine its safety and efficacy for a new use. Communication with FDA staff.

[3] 21 U.S.C. section 355(a); FFDCA section 505(a). This paragraph is taken from R. Merrill and P. Hutt, FOOD AND DRUG LAW CASES AND MATERIALS 404 (1980).

prohibits the interstate shipment of any drug that lacks an approved NDA. Congress therefore enacted section 505(i) of the FFDCA to enable sponsors of new drugs to conduct the testing necessary to support an NDA. This section authorizes FDA to exempt a drug from the prohibition against interstate shipment and from certain other statutory requirements while that drug is undergoing clinical investigations. The request for such an exemption is most formally called a "Notice of Claimed Investigational Exemption for a New Drug," or "IND." The term "IND" was so commonly thought to mean "Investigational New Drug Application" that in 1987 regulations were promulgated to define IND to mean just that.[4]

The drug development process is generally thought to consist of three phases of human testing to determine if a drug is safe and effective.[5] In Phase 1, the total number of patients varies with the drug; however, the number is generally in the range of 20-80 subjects.[6] The drug is tested to determine how it is tolerated, metabolized, and excreted.[7] In Phase 2 the drug is tested in no more than several hundred patients who participate in controlled clinical trials.[8] Data from these trials are used to evaluate the drug's safety and efficacy.[9] In Phase 3 the drug is tested in anywhere from several hundred to several

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[4]Communication with FDA staff.

[5] 53 Fed. Reg. 41518 (October 21, 1988).

[6]21 C.F.R. section 312.21(a).

[7]53 Fed. Reg. 41518.

[8]21 C.F.R. section 312.21(b).

[9]53 Fed. Reg. 41518.

thousand patients.[10] The safety and efficacy data obtained in this phase are used to evaluate the overall benefit-to-risk relationship of the drug and to provide information for drug labeling.

This description of the drug development process is simplistic; in reality the phases of testing may overlap. Moreover, it should be noted that "[t]he three phases describe the usual process of drug development, but they are not statutory requirements. The basis for marketing approval is the adequacy of the data available; progression through the particular phases is simply the usual means the sponsor uses to collect the data needed for approval..."[11]

REGULATIONS GOVERNING INVESTIGATIONAL NEW DRUG APPLICATIONS

FDA has promulgated detailed regulations governing the use of investigational new drugs, including procedures and requirements for the submission of investigational new drug applications (INDs).[12] An investigational new drug for which an IND has been filed is

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[10] 21 C.F.R. section 312.21(c).

[11] 53 Fed. Reg. 41518 (October 21, 1988).

[12] 21 C.F.R. section 312.1(a). See generally 21 C.F.R. Part 312 for the regulations pertaining to Investigational New Drug Applications. Those regulations define "IND" to mean "investigational new drug application." "IND" is synonymous with the previously used term, "Notice of Claimed Investigational Exemption for a New Drug." 21 C.F.R. section 312.3(b).

The term "IND" is used to refer not only to the application itself, but to the entire file of requests, protocols, and data submitted to FDA in the course of drug development. In contrast the investigational new drug is termed "IND drug." Communication with FDA staff.

exempt from the premarketing approval requirements contained in the Act, including the prohibition against the interstate shipment of drugs lacking an approved NDA.[13] In addition the IND regulations set forth rules about promoting and charging for investigational drugs;[14] the required contents of the IND application,[15] including protocol requirements;[16] the filing of IND safety reports[17] and annual reports;[18] the emergency use of an investigational new drug;[19] and the responsibilities of sponsors and investigators.[20] For purposes of this report, the sections of the IND regulations that set forth the rules about charging for investigational new drugs and the role of Institutional Review Boards (IRBs) are most significant.

Charging: The regulations state that sponsors may not charge for investigational new drugs without FDA's permission, and that the agency's permission will not be granted without good reason:

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[13] The regulations provide: "An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug." 21 C.F.R. section 312.1 (a).

[14] 21 C.F.R. section 312.7.

[15] 21 C.F.R. sections 312.20 through 312.38.

[16] 21 C.F.R. sections 312.23(a)(6) and 312.30.

[17] 21 C.F.R. section 312.32.

[18] 21 C.F.R. section 312.33.

[19] 21 C.F.R. section 312.36.

[20] 21 C.F.R. sections 312.50 through 312.70.

> Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.[21]

The rule articulates FDA's view that the expense of distributing drugs in the course of conducting clinical trials is a normal cost of doing business. The sponsor is expected to assume this burden and will not be allowed to charge absent a demonstration of economic necessity.[22]

IRB Approval: The regulations[23] require every Investigational New Drug Application to include:

> A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of Part 56.[24]

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[21] 21 C.F.R. section 312.7(d).

[22] R. Levine, FDA's New Rule on Treatment Use and Sale of Investigational New Drugs, 9 IRB 1,3 (July/August 1987).

[23] FDA regulations define an Institutional Review Board, or "IRB," as "any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act." 21 C.F.R. section 56.102(g).

[24] 21 C.F.R. section 312.23(a)(1)(iv).

Once an IND is in effect, the sponsor must obtain IRB approval for any changes in existing protocols contained in the IND, and for any new protocols submitted under an existing IND.[25] In addition, the sponsor must submit any protocol amendments or new protocols to FDA for review.[26] Sponsors are also required to obtain from investigators signed statements that include, among other provisions, a commitment by the investigator that an IRB will be responsible for the "initial and continuing review and approval of the clinical investigation...."[27] The investigator's responsibilities are reiterated in a section of the regulations entitled "Assurance of IRB review:"

> An investigator shall assure that an IRB that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.[28]

Treatment INDs

In May of 1987 FDA promulgated its "Treatment IND Regulations," which comprise three sections of the IND regulations.[29] Treatment INDs are distributed for the dual purpose

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[25] 21 C.F.R. section 312.30.

[26] Id.

[27] 21 C.F.R. section 312.53 (c)(1)(vii).

[28] 21 C.F.R. section 312.66.

[29] 52 Fed. Reg. 19466 (22 May 1987); codified at 21 C.F.R. sections 312.7, 312.34, and 312.35.

of providing promising new drug treatments to desperately ill patients and obtaining additional safety and efficacy data about the drug.[30] The "Treatment IND" must meet four criteria:

- The drug is intended to treat a serious or immediately life-threatening disease;
- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population.
- The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.[31]

Drugs designated as Treatment INDs must have demonstrated some evidence of effectiveness during the testing process.[32] (Figures 2.1 and 2.2 show a list of approved Treatment INDs that have not yet obtained approved NDAs and those with NDA approval.)

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[30] 21 C.F.R. section 312.34(a).

[31] 21 C.F.R. section 312.34(b)(1).

[32] Letter from Hugh C. Cannon, Associate Commissioner for Legislative Affairs, FDA, to Congressman Ted Weiss, Chairman, Subcommittee on Human Resources and Intergovernmental Relations of the Committee on Government Operations, dated 28 June 1989; 52 Fed. Reg. 19476 (22 May 1987), 21 C.F.R. section 312.34.

FIGURE 2.1

APPROVED TREATMENT IND'S

DRUG	INDICATION	SPONSOR	PATIENTS TREATED TO 2-90	ALL STUDIES COMPLETE WHEN TREATMENT IND STARTED	TREATMENT IND APPROVAL DATE	NDA SUBMITTED
CMV IG	Prevent CMV in renal transplant patients	Mass.	166	Y	10-87	Y
Trimetrexate	PCP, intolerant to other therapy	NIAID	193	N	2-88	N
Pentostatin	Hairy cell leukemia refractory to interferon	NCI	91	Y	7-88	N
Teniposide	Relapsed or refractory acute lymphoblastic leukemia	NCI	27	Y	10-88	N
Levamisole	Adjuvant Rx with 5FU, Duke's C Colon Cancer	NCI	2218	Y	5-89	Y
Erythropoietin	AZT related anemia	Ortho	650	N	6-89	Y
Exosurf	Pre-term infants with risks of RDS	Burroughs-Wellcome	4425	Y	7-89	Y
DDI	AIDS or ARC intolerant to AZT	Bristol	5625	N	9-89	N
Survanta (bovine plum. surfactant)	Prevention + Rx of RDS in premature infants	Ross Labs	771	Y	9-89	Y
Retrovir	Pediatric patients with HIV	Burroughs-Wellcome	281	Y	10-89	Y
Ceredase	Gaucher's Disease Type I	Genzyme	3	N	11-89	N
Fludarabine phosphate	Chronic Lymphocytic Leukemia	NCI	278	Y	11-89	N
Baclofen Intrathecal	Spasticity	Medtronic	NA	NA	3-90	N

SOURCE: Robert J. Temple, M.D., Director Office of Drug Research and Review, FDA, March 1990.

FIGURE 2.2

APPROVED TREATMENT IND'S
THAT HAVE NDA APPROVAL

DRUG	INDICATION	SPONSOR	PATIENTS TREATED TO NDA	ALL STUDIES COMPLETED WHEN TREATED IND STARTED	NDA SUBMITTED WHEN TREATMENT IND STARTED	TREATMENT IND APPROVAL DATE	NDA APPROVAL DATE
Ifosfamide/ Mesna	Refractory Testicular Cancer	NCI	18	Y	N	12-87	12-88
Clomipramine	Severe Ob-Com Disease	Ciba	1574	Y	N	6-88	12-89
Selegiline	Parkinson's Disease with incomplete response to other agents	Somerset	534	Y	Y	6-88	6-89
Ganciclovir	Sight threatening CMV retinitis	NIAID	1136	N	(Y)	11-88	6-89
Pentamidine Aerosol	PCP prevention in high-risk HIV	Lypho-Med	728	(Y)	(Y)	2-89	6-89

(Y) = yes but interim or incomplete

SOURCE: Robert J. Temple, M.D., Director Office of Drug Research and Review, FDA, March 1990.

Charging: A sponsor or investigator may charge for a Treatment IND provided certain criteria are met. The relevant portion of the regulation reads:

> (2) Treatment protocol or treatment IND.[33] A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under section 312.31.
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> Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.[34]

These provisions "reflect FDA's basic premise that treatment use is intended to provide therapy for desperately ill patients and that drug manufacturers should not be expected to subsidize such therapy."[35] To date three of eighteen sponsors have charged for Treatment IND drugs.[36]

IRB Approval: As for all INDs, the sponsor or investigator of a Treatment IND is required by regulation to obtain IRB approval for its use. The regulations state in relevant part: "Safeguards. Treatment use of an investigational drug is conditioned on the sponsor and

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[33] A "treatment IND" is a special case where the only protocol under the IND is the treatment protocol. FDA Clinical Investigator Information Sheets, "Treatment Use of Investigational Drugs," p.29 (May 1989).

[34] 21 C.F.R. section 312.7(d)(2).

[35] R. Levine, FDA's New Rule on Treatment Use and Sale of Investigational New Drugs, 9 IRB 3 (July/August 1987).

[36] The Massachusetts Department of Public Health charged for CMV immune globulin; Somerset Pharmaceuticals charged for Deprenyl; and Lyphomed charged for Pentamidine.

investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 C.F.R. Part 50) and institutional review boards (21 C.F.R. Part 56)..."[37] It is possible, however, to obtain waivers in appropriate cases from FDA under the IRB regulations (21 C.F.R. section 56.105). [38]

Group C Cancer Drugs

In addition to Treatment INDs, there exists another important category of investigational drugs available for potentially widespread treatment use outside of clinical trials: Group C cancer drugs. This category, which has not been defined in regulations, was developed jointly by the National Cancer Institute (NCI) and FDA. In the mid-1970's, NCI and FDA recognized the need to establish a classification for the distribution of investigational agents used to treat cancer prior to their approval by FDA for commercial marketing.[39] This new classification of cancer drugs was termed "Group C," a designation indicating that these drugs were in the latter stages of development[40] and that significant amounts of data regarding their safety and efficacy had been collected. (Figure 2.3 shows a list of approved Group C cancer drugs.)

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[37] 21 C.F.R. section 312.34(c). (Emphasis added.)

[38] 52 Fed. Reg. 19470 (May 22, 1987).

[39] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (January 1990), 1.

[40] FDA described the Group C category in a memorandum dated 3 August 1977 as those drugs "which are in Phase III or through Phase III..." Id. at 2. Phase III refers to the third, or last of the three phases of human testing that comprise the drug development process.

FIGURE 2.3

DIVISION OF CANCER TREATMENT. NCI

GROUP C AGENTS

DRUG	Date IND	Group C	NDA Approval	Withdrawn
Lomustine	2/68	4/76	10/76	
Carmustine	6/63	4/76	5/77	
Semustine	1/71	8/76	--	7/83
Daunorubicin	12/65	8/76	5/80	
Asparaginase (E. coli)	1/68	10/76	4/78	
Cisplatin	7/71	7/77	12/78	
Streptozotocin	3/67	8/76	5/82	
5-Azacytidine	1/71	8/76	--	
Asparaginase (Erwinia)	3/71	2/78	--	
Hexamethylmelamine	6/63	7/77	--	
Etoposide	9/72	5/78	10/83	
Amsacrine	8/77	12/81	--	
THC	9/78	10/80	5/86	
IL-2/LAK	2/84	5/87	--	
Ifosfamide/Mesna	11/87	12/87	12/88	
Deoxycoformycin	6/79	7/88	--	
VM-26	9/72	10/88	--	
Levamisole	2/77	5/89	--	
Fludarabine Phosphate	11/82	10/89	--	

SOURCE: "Group C Anticancer Drugs, "Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, January 1990.

To place a drug in Group C, NCI submits data demonstrating its safety and effectiveness to FDA.[41] Both FDA staff and the FDA's Oncologic Drugs Advisory Committee review the data.[42] For an agent to be classified as a Group C agent, "there must be wide spread (sic) consensus that effectiveness has been demonstrated for a specific malignancy."[43] Group C agents are always made available free of charge.[44]

OTHER INVESTIGATIONAL DRUGS

For purposes of this report, Treatment INDs and Group C cancer drugs constitute the two major categories of drugs that FDA has permitted to be used for treatment purposes before the drugs have received marketing approval pursuant to the NDA process. Historically, however, several other terms have emerged to describe unapproved drugs that have been designated for treatment use in certain situations. These terms include "open protocols," "open labels," "compassionate use," and "emergency INDs." More recently the term "parallel track" has also emerged to describe situations where investigational drugs are made available for treatment use outside of research settings.[45] The purpose of the Treatment IND Regulations was to formalize the procedures under which FDA had permitted distribution of unapproved drugs for treatment purposes. However, some of the situations

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[41] Id. at 1.

[42] Id.

[43] Id.

[44] Id. at 5.

[45] 55 Fed. Reg. 20856 (May 21, 1990).

described by these historical terms do not fall within the scope of the current Treatment IND Regulations.

Open Protocols and Open Labels

The FDA has neither a program nor regulations that deal specifically with "open protocols." An open protocol is simply one type of study normally carried out under an Investigational New Drug Application. Open protocols are initiated, as is any study under an IND, when the sponsor submits a protocol pursuant to the IND.[46] While "open" technically means unblinded, the term is generally used to mean an uncontrolled study, typically carried out to obtain safety information, especially over the long-term. It is common, for example, to have "open extensions" of controlled trials in which patients who appear to have responded well to the test drug in the controlled trial continue to receive the drug and to be closely monitored.[47]

The majority of commercial INDs have open studies in them; it is usual for the majority of the patients reported in an NDA to have received the drug in open protocols, rather than in controlled trials. Open studies under an IND have all the features of any other protocol (other than those related to control groups, blinding, etc.), but the specifics of these features

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[46] Letter from Cannon to Weiss dated 28 June 1989.

[47] Id.

vary from drug to drug and study to study. The features that typically characterize open protocols include: specific eligibility criteria; identified investigators; a planned number of patients; provisions for close, specified monitoring of patients; and enrollment through typical in-hospital or outpatient sources. Many open studies are relied on to establish a drug's safety but not its effectiveness. Evidence of both safety and efficacy is required for FDA approval.

The term "open label" has been used synonymously with the term "open protocol."[48]

"Compassionate Use"

"Compassionate use" INDs are not formal controlled trials or open safety studies. It is a term for uses that are outside the main development of the drug, that may be "premature,"[49] and that generally involve only a few patients.[50]

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[48]Communication with FDA staff.

[49] The "compassionate use" of drugs may be considered "premature" if there exists little evidence that the proposed therapy is useful. In such cases use of the drug is based on theoretical grounds or on anecdotes of success. See FDA Clinical Investigator Information Sheets, "Treatment Use of Investigational Drugs," at 34 (May 1989).

[50] "Compassionate use" is not a program and is a term that FDA does not officially sanction. However, the long history of use of this term, both inside and outside the FDA, makes it difficult to eliminate. The term has the unfortunate implication that some uses of drugs are "compassionate", while others, such as those done in formal studies, are bureaucratic and indifferent to the needs of patients.

"Compassionate uses" occur from time to time when FDA receives requests from physicians to use a specific drug for an individual patient who has exhausted all other treatment alternatives. Often there is little evidence supporting the use; sometimes there is only a hypothesis. These situations are really open "pilot" studies, which are typically carried out by knowledgeable physicians and involve one or a very small number of patients. If successful, they may be followed by a more formal development program. FDA tries to ensure that these pilot programs do not evolve into an extensive distribution for an unevaluated use.[51]

Emergency INDs

Emergency INDs are defined in regulation.[52] They can apply to any kind of IND and are used "in an emergency situation that does not allow time for submission of"[53] a written IND. In such cases "FDA may authorize shipment of the drug for a specified use in advance of submission of an IND."[54] The request is made by telephone "or other rapid communication means,"[55] and a written submission is made as soon after the telephone request as possible.

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[51] Letter from Cannon to Weiss dated 28 June 1989.

[52] 21 C.F.R. 312.36.

[53] Id.

[54] Id.

[55] Id.

Parallel Track

The "parallel track" concept has been developed by the Public Health Service "to expand the availability of promising investigational agents and to make these agents more widely available to people with AIDS and HIV-disease who have no therapeutic alternatives and who cannot participate in the controlled clinical trials."[56] Under this proposed policy, two types of studies would be conducted concurrently, or "in parallel:" (1) controlled clinical investigations, and (2) studies lacking concurrent control groups.[57]

The parallel track concept differs from the Treatment IND category in two ways: (1) parallel track, as proposed, is limited to individuals with AIDS or HIV-related diseases;[58] and (2) drugs made available pursuant to the parallel track mechanism might have less evidence of effectiveness than that generally required for a Treatment IND drug.[59]

As is the case for all investigational uses of drugs, FDA has authority for approving and monitoring the study protocols that are developed pursuant to the proposed policy of expanded availability for AIDS investigational drugs.[60]

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[56]55 Fed. Reg. 20856 (May 21, 1990). The complete proposed policy statement of the Public Health Service on the "parallel track mechanism" is found at 55 Fed. Reg. 20856 through 20860 (May 21, 1990).

[57]Id. at 20857.

[58]Id. at 20856.

[59]Id. at 20857.

[60]Id. at 20857. See 55 Fed. Reg. 20802 et seq. for a proposed regulation detailing FDA's authority to terminate clinical studies of IND drugs or place the studies on clinical hold.

STANDARDS FOR SAFETY AND EFFECTIVENESS

Under the Federal Food, Drug, and Cosmetic Act, a drug approved for marketing must be safe and effective for its intended use.[61] The IND regulations do not specify the level of safety and effectiveness that an investigational drug must demonstrate, since the drugs are undergoing investigation for the purpose of determining their safety and effectiveness. The clinical trials conducted pursuant to an IND are intended to produce the relevant data necessary to support a new drug application (NDA). The IND regulations do, however, articulate the following "general principles:"

> (a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.
>
> (b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.[62]

The Treatment IND regulations contain two specific standards, written as bases for rejecting a Treatment IND request: one for "serious" diseases and one for "immediately life-threatening" diseases:

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[61] 21 U.S.C. section 355(b); FFDCA section 505(b).

[62] 21 C.F.R. section 312.22(a) and (b).

> Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.
>
> Immediately life-threatening disease. (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:
> (A) May be effective for its intended use in its intended patient population; or
> (B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. [63]

With respect to Group C drugs, the current guidelines for distribution contain two criteria:

> a.Evidence of safety and relative efficacy in the treatment of patients with a specific cancer type in the form of published abstracts, papers, and reports to the NCI.
> ...
>
> c.Relative efficacy, demonstrable by schedule and doses that are safely administered by properly trained physicians without requiring specialized supportive care facilities. This review is to be based on available published or unpublished data and without the need for additional supportive survival data. It is not tantamount to formal FDA approval of effectiveness for this indication. [64]

SUMMARY OF MAJOR CHARACTERISTICS OF CATEGORIES

The following section summarizes the major characteristics of the two categories of investigational drugs available for treatment use: Treatment INDs and Group C cancer drugs. It then compares them to drugs made available pursuant to a regular IND.[65],[66]

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[63] 21 C.F.R. Section 312.34(b)(2) and (b)(3).

[64] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (January 1990), 4. (Emphasis added.)

[65] This report will treat Group C cancer drugs and Treatment INDs as separate categories in order to compare them. It should be noted, however, that in July of 1988 FDA began to treat NCI applications for Group C status as Treatment IND requests and to review them under the standards set forth in the Treatment IND regulations. Such drugs are designated Treatment IND/Group C drugs. NCI and FDA are currently discussing

1. **Existence of Regulations:** Treatment INDs are defined in regulations promulgated in May of 1987.[67] As noted above, these regulations comprise three sections of the IND regulations.[68] No regulations have been promulgated to define Group C cancer drugs.

2. **Availability Limited to Serious or Life-Threatening Diseases:** The regulations defining Treatment INDs specify that the drug must be "intended to treat a serious or immediately life-threatening disease." [69] Although no regulations have been promulgated to govern the treatment use of Group C cancer drugs, the commentary accompanying the promulgation of the Treatment IND regulations states that "most advanced metastatic refractory cancers" would "normally be considered to be immediately life-threatening...." [70] Group C cancer drugs are therefore used to treat a disease that, in its advanced stages, has been classified as immediately life-threatening. In contrast, the use of regular INDs is not restricted to the treatment of serious or life-threatening diseases.

3. **Charging for the Drug:** As noted above, FDA will not permit the sponsor of a regular IND to charge for the drug unless the sponsor can demonstrate why charging is necessary for the sponsor to begin or continue the study. The sponsor may charge for a Treatment

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this practice. FDA's reason for combining the categories was straightforward: "Group C was developed in an informal way but deals with situations now encompassed by the Treatment IND regulation." Memorandum from Robert Temple, M.D., Director, FDA Office of Drug Evaluation I, to John Palmer, M.D., Director, FDA Division of Oncology and Radiopharmaceuticals, dated 14 July 1988.

[66] The term "regular IND" is used in this report to mean a drug made available pursuant to an IND. The adjective "regular" is used to distinguish such a drug from a Treatment IND.

[67] 21 C.F.R. sections 312.7, 312.34 and 312.35. See also 52 Fed. Reg. 19466 et seq. (May 22, 1987).

[68] 21 C.F.R. Part 312.

[69] 21 C.F.R. section 312.34(b)(1)(i).

[70] 52 Fed. Reg. at 19467.

IND, provided that the criteria specified in the regulations are met.[71] Group C agents are always made available free of charge.[72]

4. **Research Protocol Eligibility Criteria:** A typical investigational new drug application contains multiple protocols. The entry criteria contained in the protocol for a controlled trial usually differ from the entry criteria contained in an open-label protocol.[73]

Under the Treatment IND Regulations, patients must meet the criteria specified in the Treatment IND protocol.[74] If the controlled study is still enrolling patients, the Treatment IND will normally be limited to patients not eligible for the controlled study.[75] Patients receiving Group C cancer drugs must be eligible for the Group C protocol.[76]

5. **Special Qualifications of Physicians, Sponsors, and Investigators:** The IND regulations require sponsors to "select only investigators qualified by training and experience as appropriate experts to investigate the drug."[77] The Treatment IND regulations, which comprise a part of the IND regulations, refer to the "safeguards of the IND process," including the requirement of "distribution of the drug through qualified experts...."[78] Treatment INDs, like regular INDs, would always be administered by a qualified physician,

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[71] 21 C.F.R. section 312.7(d)(2).

[72] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (January 1990), 5.

[73] Communication with FDA staff.

[74] 21 C.F.R. section 312.25(a)(1)(iii) and (b)(1)(iv).

[75] Communication with FDA staff.

[76] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (January 1990), 5.

[77] 21 C.F.R. section 312.53 (a). See also 52 Fed. Reg. 19469 (May 22, 1987).

[78] 21 C.F.R. section 312.34(c).

but he or she might have less specialized training than the physicians who conduct large controlled trials pursuant to the protocols contained in regular INDs.[79] Enrollment of patients onto Treatment INDs would therefore be available to specialists practicing in the community, while regular INDs are more typically administered by academic physicians practicing in a research institution.[80]

Physicians who obtain Group C drugs for their patients "must be board eligible/certified oncologists or hematologists or specialists such as urologists and gynecologists who routinely treat cancer patients." [81]

6. **IRB Approval:** IRB approval is always required for INDs, Treatment INDs, and Group C cancer drugs, unless the requirement is waived by FDA.[82] However, the IRB of an individual institution may still require local review even if FDA has granted a waiver to the drug's sponsor.

7. **Reporting Requirements, Including Adverse Reactions:** The IND regulations require sponsors to submit safety reports on all INDs.[83] This requirement applies to Treatment

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[79] Communication with FDA staff.

[80] Communication with FDA staff.

[81] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (1990), 5. This publication also states: "Group C drugs are provided to properly trained physicians who have registered via Form FD-1572 for the treatment of individual patients who qualify under the conditions of "The Guidelines" for the drug." Id. at 3.

[82] See 21 C.F.R. section 56.105.

[83] 21 C.F.R. section 312.32.

INDs.[84] The rules for distribution of Group C drugs also require sponsors and investigators to report adverse reactions.[85]

Figure 2.4 summarizes the characteristics of INDs, Treatment INDs, and Group C cancer drugs discussed above.

DISCUSSION

FDA's drug approval process divides drugs into two very broad categories: drugs that are approved for marketing and therefore by definition have an approved NDA; and drugs that have not been approved for marketing. In theory these unapproved drugs are distributed only for use in clinical trials pursuant to protocols contained in their investigational new drug applications (INDs).

Historically, however, there have emerged a number of terms to describe situations where FDA has authorized the use of unapproved drugs for treatment purposes outside of clinical trials, but still under the auspices of an IND. With the promulgation of the Treatment IND Regulations in May of 1987, FDA formalized the procedures under which it had permitted the distribution of unapproved drugs for treatment purposes.

Treatment INDs have thus emerged as a formal, intermediate category between clinical investigation and marketing approval. FDA has characterized a treatment protocol

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[84] 21 C.F.R. section 312.34(c).

[85] An FDA memorandum dated 3 August 1977 describes the Group C category and states: "The physicians are required to report adverse reactions to NCI but not efficacy." Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Group C Anticancer Drugs, (January 1990), 2.

FIGURE 2.4

CHARACTERISTICS OF INVESTIGATIONAL DRUGS AVAILABLE FOR TREATMENT USE

	Category set forth in Regulations?	Limited to serious or life-threatening diseases?	May the Sponsor charge?	Must Patient meet protocol elig. criteria to rec. drug?	Are Physicians selected based on expertise?	Is IRB approval necessary?*	Are there reporting requirements including adverse reactions?
Regular IND	Yes	No	Yes	Yes	Yes	Yes	Yes
Group C	No	Yes	Not Applicable	Yes	Yes	Yes	Yes
Treatment IND	Yes	Yes	Yes if criteria are met	Yes	Varies**	Yes	Yes

* For all three categories, IRB approval is always required unless waived by FDA. Even then, the local institution may require it.

** Depends on the likelihood of adverse reactions and on the conditions required for the drug's administration.

submitted pursuant to the Treatment IND regulations as "a bridge between the completion of early stages of clinical trials and final marketing approval."[86]

Treatment INDs are made available at an intermediate point in the development process; they are more widely available for treatment use than regular INDs, but are not as widely distributed as drugs having approved NDAs.

Of all the investigational drug categories discussed above, Treatment INDs and Group C drugs differ in several significant respects from investigational drugs distributed in clinical trials pursuant to the IND regulations. The important differences between Treatment INDs and Group C drugs, on the one hand, and all other investigational drugs, on the other hand, include: (1) the purpose for which they are released; and (2) the stage of development at which they are released.

These differences between Treatment INDs and other investigational drugs raise two questions with important implications for coverage policy:

1. Is the primary purpose of distributing the drug to obtain research data or to provide treatment?

2. Is there identical evidence of safety and effectiveness for all drugs that have been designated as Treatment INDs?

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[86] 53 Fed. Reg. 41517 (October 21, 1988). The Treatment IND regulation itself states:

> In the case of a serious disease, a drug ordinarily may be made available for treatment use under this section during Phase III investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase II. In the case of an immediately life-threatening disease, a drug may be made available for treatment use under this section earlier than Phase III, but ordinarily not earlier than Phase II.

21 C.F.R. section 312.34(a). (Emphasis added.)

1. **Is the primary purpose of distributing the drug to obtain research data or to provide treatment?** Treatment IND drugs are distributed for a dual purpose, which is best expressed in the Treatment IND Regulations: "The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness.[87] Pursuant to the Federal Food, Drug, and Cosmetic Act, FDA's authority for permitting distribution of an unapproved drug is to facilitate the sponsor's collection of safety and efficacy data.[88] Thus, as articulated in the regulation, Treatment IND drugs are distributed in part for research purposes. However, Treatment INDs have a second purpose, which distinguishes them from other INDs: they provide therapy for "desperately ill patients." As their name implies, Treatment INDs are distributed to facilitate both research and treatment, but the treatment component is at least as strong as the research purpose. In this respect, Treatment INDs differ from regular INDs, which are distributed primarily for research purposes, i.e., to obtain safety and efficacy data.

Two features of the Treatment IND Regulations clarify this emphasis on treatment. The provisions of the regulations dealing with charging and with IRB review underscore the treatment purpose of Treatment INDs. The provisions that permit sponsors to charge for Treatment INDs, provided certain criteria are met, reflect the fact that such drugs are considered to be therapy for the patients who receive them, and that the expense of therapy is not a research cost that should be borne by the drug's sponsor. [89] Stated differently, if the purpose of drug distribution is therapy, then patients should be responsible for its cost as they are for other therapeutic interventions; if the purpose is research, then the cost of distributing the drugs constitutes a normal business expense that the sponsor ought to bear.

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[87] 21 C.F.R. section 312.34(a).(Emphasis added.)

[88] 21 U.S.C. section 355(i); FFDCA section 505(i).

[89] R. Levine, FDA's New Rule on Treatment Use and Sale of Investigational New Drugs, 9 IRB at 3 (July/August 1987).

Thus the presumption underlying the charging provisions of the Treatment IND regulations is the reverse of the presumption behind the relevant provisions of the IND regulations.[90]

The availability of waiver of IRB review is another distinction between Treatment INDs and regular INDs. In a proposed version of the Treatment IND Regulations, FDA stated its willingness to waive generally the IRB review requirement for Treatment INDs. [91] In response to comments, however, FDA removed the presumption of IRB waiver from the final rule. [92] In the preamble to the final rule the agency emphasized nonetheless that "although the treatment IND provisions do not solicit waiver requests, waivers in appropriate cases are still available from FDA under the IRB regulations (21 CFR 56.105)." [93] This waiver provision is important: to date FDA has granted IRB waiver for eleven of seventeen Treatment INDs and for ten of nineteen Group C cancer drugs. [94]

2. **Is there identical evidence of safety and effectiveness for all drugs that have been designated as Treatment INDs?** The answer to this question is no. Certain drugs had completed all their clinical trials at the time they were made available for treatment use,

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[90] Id. Another reason why some sponsors feel the need to charge for Treatment IND drugs is because such drugs are available to potentially large numbers of patients who meet the stated criteria. Some sponsors cannot afford this additional cost. In contrast, regular IND drugs are distributed for treatment to limited numbers of patients in clinical trials. (Communication with NCI staff.)

[91] 52 Fed. Reg. 19469 (May 22, 1987).

[92] Id. at 19470.

[93] Id.

[94] Communication with FDA staff, Office of Health Affairs. The total number of waivers granted is sixteen, not twenty-one, because five of the Group C waivers are also designated as Treatment IND waivers. This dual designation results from FDA's policy of combining Group C and Treatment IND applications into one category: Treatment IND/Group C.

FDA will only waive the IRB review requirement if the patients' rights are protected by an alternative mechanism. For example, when NCI applies for a waiver of local IRB review for a Group C drug, that particular Group C treatment protocol undergoes careful and thorough central IRB review at NIH in order to assure that proper ethical standards are maintained for informed consent and study design. This allows local IRBs to rely on the central NIH IRB review rather than repeating this review. The IRB waiver provisions are intended to speed a patient's access to the drug.

while others were made available before Phase 3 trials had been completed. Figures 2.1 and 2.2 indicate whether all studies had been completed when the specific Treatment IND designation started.

The fact that different Treatment IND drugs have been made available at different stages of investigation does not imply any laxness on FDA's part; nor does it mean that a different standard was applied to different drugs. Since Treatment IND drugs were intended to serve as a "bridge" category in the drug development process, it is logical that different Treatment IND drugs would have differing amounts of safety and efficacy data. Certain drugs have been designated as Treatment IND drugs when they were close to obtaining approval of their NDA. Others have been made available at an earlier point in the investigational process, but at a time when, in FDA's judgment, the available data were adequate to justify their treatment use. There is thus not one specific amount of data that will justify designating an investigational drug for treatment use, but a range. In addition, as permitted by the Treatment IND Regulations, two other factors influence the decision: the severity of the disease, and the existence of alternative therapies.

There is another reason why different Treatment IND drugs have been made available at different stages of development. The amount of data depends in part on the drug's stage of development at the time the drug's sponsor submits the application for Treatment IND status. A sponsor must request FDA to designate a particular drug as a Treatment IND drug; FDA does not take such an action on its own initiative.[95] Consequently some of the differences in the amount of data available to support different Treatment IND drugs reflect choices of the sponsors.

To summarize: Treatment IND drugs are designated at different stages of clinical investigation; some are close to obtaining marketing approval, while others are at

[95]21 C.F.R. section 312.35(a).

considerably earlier stages of the investigational process. In addition, a range of data is considered acceptable to support the designation of a drug as a Treatment IND drug.

CHAPTER THREE:
MEDICARE COVERAGE POLICY FOR DRUGS

This chapter presents a brief history of HCFA's drug coverage policy and analyzes the relationship between FDA drug regulation and HCFA coverage for investigational drugs.

BACKGROUND

The Medicare program was established by Congress in 1965 with the enactment of title XVIII of the Social Security Act (the Act). The program provides payment for health care provided to persons 65 years of age or older, disabled beneficiaries, and persons with end-stage renal disease. The program currently covers approximately 30 million aged, 3 million disabled individuals, and 130,000 persons with end-stage renal disease.

The Medicare program consists of two separate but complementary insurance programs: the Hospital Insurance Program (Part A) and the Supplementary Medical Insurance Program (Part B). Part A benefits include medical services furnished by inpatient hospitals, extended care facilities, home health agencies, and hospices. Part B covers a wide range of medical services and supplies such as those furnished by physicians or others in connection with physicians' services, outpatient hospital services, and outpatient physical and occupational therapy services. Part B also covers certain drugs and biologicals that cannot be self-administered, diagnostic x-ray and laboratory tests, durable medical equipment, prosthetic devices, ambulance services and certain medical supplies.

While the Medicare law provides coverage for the broad categories of benefits described above, it also places categorical limitations on the coverage of the services furnished by certain health care practitioners, such as dentists, chiropractors, and podiatrists, and it specifically excludes some categories of services from coverage, such as cosmetic surgery, personal comfort items, custodial care, and routine physical checkups.

The Medicare law does not, however, provide an all-inclusive list of specific items, services, treatments, procedures or technologies covered by Medicare. The intention of Congress, at the time the Medicare law was enacted in 1965, was that Medicare would provide health insurance to protect the elderly or disabled from the substantial costs of acute health care services, principally hospital care. However, Congress recognized that questions about coverage of specific services would invariably arise and would require a specific decision of coverage by those administering the program. Thus, it vested in the Secretary the authority to make those decisions under section 1862(a)(1)(A) of the Act, commonly referred to as the "reasonable and necessary" provision.

Section 1862(a)(1)(A) states:

> Notwithstanding any other provisions of this title, no payment may be made under Part A or Part B for any expenses incurred for items or services which . . . are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

This is a key provision since the words "[n]otwithstanding any other provision of this title . . . " make this an overriding exclusion that may be applicable in a given situation despite the existence of provisions that would otherwise permit coverage. Thus, while Congress provided for the coverage of services such as inpatient hospital care and physicians' services, coverage for those services is prohibited unless they are "reasonable and necessary."

Historically, HCFA has interpreted the "reasonable and necessary" provision of the law to exclude from Medicare coverage those medical and health care services that are not demonstrated to be safe and effective by acceptable clinical evidence. In practice, Medicare contractors (that is, fiscal intermediaries, carriers, health maintenance organizations [HMOs], competitive medical plans [CMPs], and Utilization and Quality Control Peer Review Organizations [PROs]) are charged with the responsibility to assure that payments are made only for items or services that are covered under Medicare Part A or Part B.

Therefore, they must determine if a particular item or service is covered under Medicare in the course of adjudicating a Medicare claim.

Intermediary Letters 77-4 and 77-5, issued in January 1977, translated the statutory terms "reasonable and necessary" to mean that a technology is "safe" and "effective" and not "experimental" or "investigational":

> . . . a basic consideration is whether the service has come to be generally accepted by the professional medical community as an effective and proven treatment for the condition for which it is being used . . . .[I]f the service or treatment is one that is not yet generally accepted, is rarely used, novel or relatively unknown, then authoritative evidence must be obtained to establish it is safe and effective before Medicare can make payment.

NATIONAL COVERAGE CRITERIA

Current Medicare regulations (42 C.F.R. section 405.310(k)(1)) are general and do not define the terms "reasonable and necessary" or the process for how these terms must be applied. However, in April 1987[96], as part of a lawsuit settlement in Federal District Court, HCFA published a description of its coverage decisionmaking process in the Federal Register. More recently, in January 1989[97], HCFA published a notice of proposed rulemaking (NPRM) to establish criteria and procedures for national coverage decisions. The proposed rule would establish the criteria for determining whether specific health care technologies could be considered "reasonable and necessary" and therefore covered under Medicare. The proposed rule constitutes HCFA's first attempt to establish in regulations its longstanding interpretation of the statutory terms "reasonable and necessary."

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[96]52 Fed. Reg. 15560 (April 29, 1987).

[97]54 Fed. Reg. 4302 (January 30, 1989). NOTE: This study is based upon the January 1989 HCFA NPRM on Medicare coverage. It is anticipated that a final regulation will be published in 1990.

Under its proposal, HCFA would consider a service to be "reasonable and necessary" if it meets the following criteria:

- the service is safe[98] and effective;[99]
- the service is not experimental[100] or investigational;
- the service is cost-effective;
- the service is appropriate.

Figure 3.1 summarizes these criteria. All of these criteria except cost-effectiveness are currently being applied by HCFA in making national coverage decisions. Not all of the criteria are necessarily pertinent to every coverage issue and each criterion is not necessarily given equal consideration in reaching a final decision.

Cost-effectiveness is being proposed as a new criterion to be considered by contractors in making coverage decisions. Although cost-effectiveness may not be considered in every coverage decision, HCFA believes that considerations of cost are relevant in deciding whether to expand or continue coverage of technologies, particularly in the context of the current explosion of high-cost medical technologies.

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[98] "'Safe' means a judgement of the acceptability of relative risk in a specified situation." 54 Fed. Reg. 4316 (January 30, 1989).

[99] "'Effective' means the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under average conditions of use." Id.

[100] "'Experimental' means a technology that should be confined to a research setting under which human or animal subjects are assigned, in accordance with predetermined rules. A technology that is experimental is not considered safe or effective." Id.

FIGURE 3.1

HCFA PROPOSED CRITERIA FOR MEDICARE COVERAGE OF REASONABLE AND NECESSARY SERVICES

SAFE AND EFFECTIVE

- Generally accepted in the medical community as safe and effective in the setting and for the condition for which it is used
- Proven to be safe and effective based on authoritative evidence
- For breakthrough medical or surgical procedures if no safer or more effective treatments are available
- Drugs and biologicals approved for marketing by FDA
- Devices approved for marketing by FDA

EXPERIMENTAL OR INVESTIGATIONAL - NOT COVERED

- A service that is furnished for research purposes in accordance with predetermined rules
- Except for Group C cancer drugs, a drug or biological product that has not been approved under a new drug application for marketing by FDA
- A service, other than breakthrough medical or surgical procedures that are not used widely because there is inadequate evidence of safety and effectiveness

COST EFFECTIVE

- Provides significant medical benefits not otherwise available
- Less costly and at least as effective as alternative covered intervention

APPROPRIATE

- Furnished in a setting commensurate with medical needs
- Furnished by qualified personnel

Among the proposed criteria for making coverage decisions, safety and effectiveness are the key criteria. A service that is determined not to be safe and effective is not covered regardless of whether it satisfies the other criteria.[101] However, a service that is determined to be safe and effective may or may not be covered depending on whether the other criteria are met.

1. **Safety and Effectiveness:**

Services: HCFA considers a service to be safe and effective if it is generally accepted in the medical community as safe and effective in the setting and for the condition for which it is used, or is proven to be safe and effective based on authoritative evidence. A service that is safe and effective for some conditions may not necessarily be considered safe and effective for all conditions. In addition, the service must be furnished by qualified personnel.

Medical Devices: Medical devices that have been approved for marketing by FDA based on approval of a premarket approval application (PMA) or a section 510(k)[102] application submitted with clinical data are considered safe

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[101] 54 Fed. Reg. 4317.

[102] "Section 510(k)" refers to section 510(k) of the Federal Food, Drug, and Cosmetic Act. (21 U.S.C. Section 360(k)). This section establishes a procedure for determining whether a device proposed for marketing is "substantially equivalent" to a device marketed before 1976, the year of enactment of the Medical Device Amendments to the Federal Food, Drug, Cosmetic Act. If FDA determines that the device is substantially equivalent, it may be marketed without the sponsor's having to submit a premarket approval application (PMA). If FDA determines that the device is not substantially equivalent, the sponsor must submit a PMA and the device cannot be marketed until FDA approves the PMA. Flannery, Ellen, "Primer Session on Drug and Device

and effective when used for the conditions listed in the labeling of the devices.

Drugs and Biologicals: Drugs and biologicals approved for marketing by FDA are considered safe and effective for Medicare purposes when used for indications specified in their labeling.[103] In addition, FDA-approved drugs may be covered when used for indications other than those specified on their labeling as long as FDA or HCFA has not specified such use as non-approved. Coverage of non-labeled uses[104] is determined by Medicare contractors taking into consideration the generally accepted medical practice in the community.[105] The only coverage of investigational drugs is for Group C cancer drugs which are distributed by the National Cancer Institute, but have not been approved for marketing by FDA pursuant to the new drug application process.[106]

Approval Process," paper presented at the National Health Lawyers Association conference on "1989 Drugs, Devices and Biotechnology," Baltimore, MD, October 30-31, 1989.

[103]54 Fed. Reg. at 4317.

[104]"Non-labeled" uses or "off-label" uses may be defined as the "use of certain prescription drugs for conditions not named in the official labeling." 37 Fed. Reg. 16503 (August 15, 1972).

[105]54 Fed. Reg. at 4306.

[106]Id. at 4317.

Breakthrough Medical or Surgical Procedures: For these services, HCFA has indicated that the standards for safety and effectiveness are less stringent.[107] The more severe and life-threatening the illness or injury, the more acceptable a relatively less safe technology may be when no safer or more effective technologies are available. In these cases, HCFA may determine the effectiveness of a service in relation to the severity of the illness or injury it is designed to diagnose or cure and may provide coverage in certain cases, but HCFA could impose facility restrictions or patient selection criteria. HCFA also reserves the right to revise a coverage policy as additional information is obtained on the use of a particular technology.[108]

2. **Experimental or Investigational:** Medicare does not cover services that are "experimental" or "investigational," terms that HCFA uses synonymously. (This limitation is separate from the requirement of safety and effectiveness.) HCFA considers a service to be experimental or investigational if it is furnished for research purposes in accordance with predetermined rules.[109]

Drugs: A drug or biological product that has not obtained approval for marketing from FDA is considered experimental or investigational.

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[107] Id. at 4317.

[108] Id. at 4307, 4317.

[109] Id. at 4307, 4316, 4317.

Group C Cancer Drugs: Although Group C drugs have not been approved for marketing by FDA, they are covered by Medicare on an exceptions basis, if all other applicable coverage requirements are satisfied. Group C cancer drugs are not limited to clinical trials and NCI controls their distribution and use.[110] When HCFA began to cover these drugs in the early 1980s, it did so because of assurances from NCI that most Group C cancer drugs had either completed or virtually completed all of the FDA's clinical testing requirements and that in some cases the drug manufacturers had decided not to market the drug. Furthermore, NCI had determined that these drugs had shown significant evidence of effectiveness in treating one or more tumor types and that the drugs could be safely administered.[111],[112]

"Modified" Group C: Modified Group C drugs constitute a category distinct from Group C drugs. Currently, there is only one drug classified under this category--IL-2 LAK. This category requires an additional level of medical support and oversight for safe administration, and distribution by NCI is limited to qualified investigators in its network of comprehensive and cancer

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[110]Id. at 4306-7, 4317.

[111]Health Care Financing Administration, "Certain Drugs Distributed by the National Cancer Institute," Medicare Coverage Issues Manual, reprinted in Medicare and Medicaid Guide (CCH), 27, 201 (1989).

[112]Since Group C cancer drugs are almost always provided to patients at no charge, the issue is whether Medicare will cover the charges of administering the drug including the physician's fees. By explicitly covering Group C cancer drugs, HCFA is covering the cost associated with the administration of these drugs, including physicians' fees and laboratory charges deriving from the use of the drugs.

centers. Therefore, it is considered investigational and not covered by Medicare.[113]

Medical Devices: A medical device that has not been approved for marketing by FDA is considered experimental or investigational.[114]

Services: A service, other than breakthrough medical or surgical procedures for severe and life-threatening illness or injury, that is not widely used because there is inadequate evidence of safety and effectiveness is considered experimental or investigational.[115]

DISCUSSION

A review of the HCFA coverage policy raises several important issues regarding coverage of drugs:

1. Does HCFA cover drugs, devices and services in a consistent manner?
2. Does HCFA equate the use of all investigational drugs with research?

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[113]Health Care Financing Administration, "Minutes of the Coverage-Payment Technical Advisory Group," April 20, 1989, DHHS, Baltimore, MD; "Summary of Recent HCFA Actions on Modified Group C Drugs," internal HCFA staff memo, July 20, 1989.

[114]54 Fed. Reg. at 4317.

[115]Id.

3. Why does Medicare cover treatment with Group C cancer drugs, which are provided to patients at no charge, and not Treatment IND drugs?

1. Does HCFA cover drugs, devices and services in a consistent manner? HCFA appears to apply different standards of coverage for drugs, devices, and services. As highlighted in Figure 3.2, for breakthrough medical or surgical procedures, which are not regulated by FDA, HCFA has proposed that "treatments whose clinical effectiveness has not been conclusively demonstrated may be determined to be reasonable and necessary if no safer or more effective treatments are available."[116] HCFA has proposed that "the more severe and life-threatening the condition, the more likely we are to cover a treatment that has not been proven to the usual point of acceptability to us, if there are no other safe and effective treatments available."[117] Thus, for new technologies which constitute the last resort for particular patients, HCFA appears willing to weigh imperfect safety and efficacy evidence against the degree of seriousness of the illness and the availability of any safer or more effective treatments. HCFA does not apply these exceptional coverage criteria to drugs. This is similar to the rationale applied by FDA in the designation of Treatment IND drugs as indicated in Figure 3.2.

Since drugs and devices are regulated by FDA, HCFA coverage policy relies on FDA approval for marketing. In the case of devices, FDA approval is a necessary condition for coverage, but it is not sufficient. For devices, HCFA has traditionally used FDA approval as a preliminary criterion for coverage assessment, but has conducted its own review on the appropriateness of specific items for the Medicare population. For certain devices, HCFA will conduct an independent technology assessment to determine coverage for use of the device under average conditions.[118]

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[116] Id. at 4317.

[117] Id. at 4308.

[118] Id.

Medical services are not regulated by FDA; nor does there exist any formal or established evaluation system for medical services such as surgery. Therefore HCFA had to create independent criteria for safety and effectiveness. As a result of its reliance on these disparate mechanisms, HCFA may be applying de facto different coverage criteria across health care technologies.

For drugs used for their labeled indications (with the exception of Group C cancer drugs), HCFA has determined that FDA approval for marketing is sufficient evidence of safety and effectiveness for Medicare purposes. Therefore, drugs approved by FDA are covered for the indications specified in their labeling. In addition, FDA-approved drugs may also be covered when used for indications other than those specified in their labeling as long as FDA has not specified such use as non-approved. Coverage of non-labeled uses is subject to determination by HCFA's contractors, who take into consideration the generally accepted medical practice in the community.[119]

2. **Does HCFA equate the use of all investigational drugs with research?** HCFA does not cover items furnished for research purposes, or those that are experimental. Although HCFA's proposed regulation does not define research, it defines an experimental technology as one which "should be confined to a research setting... in accordance with predetermined rules."[120] In addition, HCFA indicates that "a service, other than breakthrough medical or surgical procedures, ... that is not used widely because there is inadequate evidence of safety and effectiveness is considered experimental."[121] Thus HCFA's proposed regulation equates the use of investigational drugs with research.

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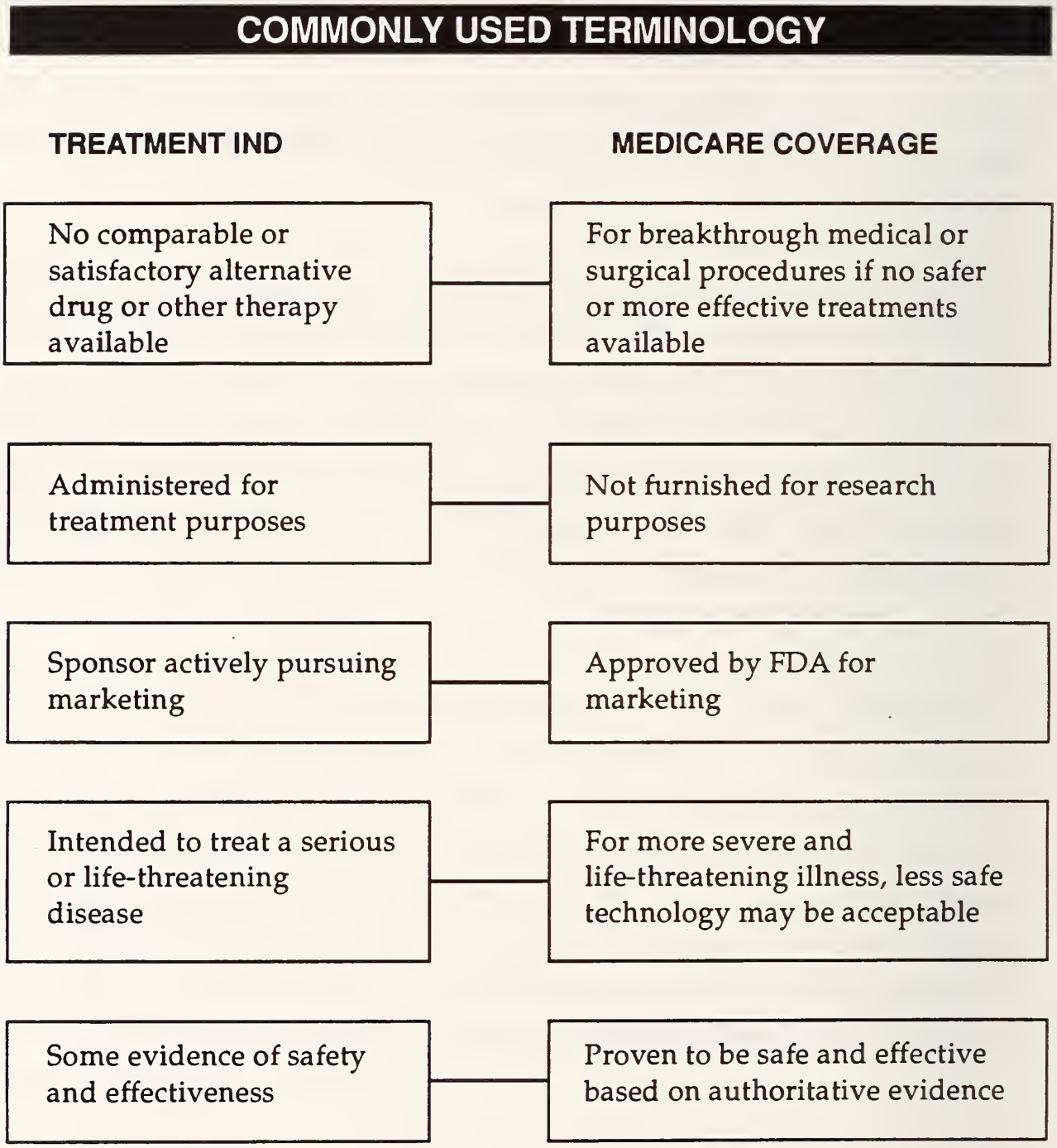
[119]54 Fed. Reg. 4306.

[120]54 Fed. Reg. at 4316.

[121]Id. at 4317.

FIGURE 3.2


COMMONLY USED TERMINOLOGY
TREATMENT IND
MEDICARE COVERAGE
No comparable or satisfactory alternative drug or other therapy available
For breakthrough medical or surgical procedures if no safer or more effective treatments available
Administered for treatment purposes
Not furnished for research purposes
Sponsor actively pursuing marketing
Approved by FDA for marketing
Intended to treat a serious or life-threatening disease
For more severe and life-threatening illness, less safe technology may be acceptable
Some evidence of safety and effectiveness
Proven to be safe and effective based on authoritative evidence

Traditionally, investigational drugs were only available (with rare exceptions) for research purposes. However, FDA has indicated that Treatment IND drugs may be used for treatment as well as investigational purposes: "During the clinical investigation of the drug it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND."[122] Treatment INDs are viewed by FDA and the provider and patient community as a source of breakthrough treatment with adequate, but less than customary, evidence of safety and effectiveness. Like Group C cancer drugs, Treatment INDs are often widely distributed and are used outside the context of a clinical trial.

HCFA has indicated that it can cover Group C drugs because they are not limited to use in clinical trials. NCI has determined that significant evidence of efficacy exists for Group C drugs and that almost all clinical testing has been completed at the time of Group C designation. Since Treatment INDs are also designated for use outside of clinical trials, and may have completed almost all clinical testing, it would appear that HCFA could apply the same standard to these drugs as it does to Group C cancer drugs. If HCFA applied safety and effectiveness criteria to all drugs without ever using FDA marketing approval as an exclusive criterion, it is possible that additional items could be determined appropriate for Medicare beneficiaries. Thus, HCFA could cover investigational drugs that are distributed for treatment purposes (i.e., Treatment IND drugs,) and continue to disallow coverage for investigational drugs that have not been approved by FDA for treatment uses.

The relevant trade-offs, however, between enhanced speed of access and reduced evidence of safety and effectiveness would need to be carefully considered. Moreover, Phase 1 and 2 testing, and often Phase 3 as well, have typically been conducted by IND sponsors upon the general population with few elderly participating. Thus, an additional issue which would require consideration is the extent to which preliminary evidence of safety and effectiveness

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[122]21 C.F.R. section 312.34(a).

for patients in the general population is directly applicable to the older population enrolled in Medicare.

3. **Why does Medicare cover Group C drugs and not Treatment IND drugs?** There is Medicare coverage for Group C cancer drugs because NCI has indicated to HCFA that these drugs "have shown significant clinical evidence of effectiveness in one or more tumor types and can be given in medical settings not requiring highly specialized supportive care," and that "these drugs had either completed or virtually completed all of the FDA's clinical testing requirements and that in many cases there was no drug manufacturer interested in marketing such drugs." [123] NCI has indicated that in the 1980's, no Group C drug has lacked a corporate sponsor.[124]

The relationship between Group C cancer drugs and Treatment IND designation is still under discussion. It is difficult to generalize about the common characteristics of the drugs in either of the two categories. FDA believes that the standard for Treatment IND designation is more demanding than for Group C drugs,[125] while NCI believes that Group C drugs differ from Treatment IND drugs in several important ways.[126] At the same time, HCFA allows coverage for Group C drugs as an exception to its coverage policy, but does not cover Treatment IND drugs. This difference of opinion about these two categories underscores the difficulty that HCFA confronts in making coverage decisions.

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[123]Internal Memo to Jackie White, Executive Secretariat, Office of the Secretary, U.S. Department of Health and Human Services, "Criteria and Procedures for Medical Services Coverage Decisions," February 22, 1990

[124]Memo to Cheryl Austein, ASPE, from Joyce O'Shaughnessy, M.D., Special Assistant, National Cancer Institute, May 30, 1990.

[125]Communication with FDA staff.

[126]According to NCI, these differences between Group C cancer drugs and Treatment IND drugs include: (1) the pursuit of marketing approval for an agent is not a requirement for Group C drugs, while it is a requirement for Treatment INDs; (2) Group C drugs are agents used only for the treatment of cancer patients; (3) Group C status is approved based on a consensus agreement between NCI, FDA and the FDA Advisory Committee; and (4) Group C agents are always provided free of charge. "Group C Anticancer Drugs", Division of Cancer Treatment, National Cancer Institute, January 1990, page 5.

CHAPTER FOUR:
OTHER GOVERNMENT AND PRIVATE SECTOR POLICIES ON INVESTIGATIONAL DRUG COVERAGE

Several recent events have provided an opportunity for public comment and analysis of the issue of coverage for investigational drugs. In addition to Medicare, this issue is under consideration by other third party-payors, drug sponsors, providers and patients:

(1) a special group was convened in 1988 by the President's Cancer Panel to review the issues of drug regulation and access to therapy;

(2) in response to HCFA's notice of the proposed rule discussed in Chapter Three, many government and private sector organizations have publicly provided their views on the issue of Medicare coverage for investigational therapies; and

(3) several private payors have begun to reevaluate their own coverage policies for investigational drugs.

OTHER GOVERNMENT POLICIES

Both NIH and FDA have expressed their concern about coverage for investigational drugs to HCFA. In addition, the Lasagna Committee has been serving as a forum for discussion of the issues surrounding earlier access to investigational therapies.

Lasagna Committee: In June 1988, then Vice-President George Bush asked the Chairman of the President's Cancer Panel, Dr. Armand Hammer, to "undertake a systematic study of drug regulation as it affects progress in developing and making available therapies for cancer and for AIDS, and make recommendations for improvements." The study was to include an examination of changes that could "accelerate the conduct of clinical trials, improve access for cancer patients to promising new treatments, and facilitate the transfer of new

therapies to medical practice."[127] In addition to the issues raised by the Vice-President, Dr. Hammer suggested that the committee "may wish to consider to what extent the federal reimbursement policies for investigational therapy, as stated in the regulations of the Health Care Financing Administration, are obstructing the development of new cancer and AIDS treatments. Should these regulations be changed to provide reimbursement for the non-research patient care costs of investigational cancer and AIDS therapies?"[128] Dr. Louis Lasagna was asked to serve as chairman of the committee which includes representatives of pharmaceutical companies, medicine, law and academia. The committee has come to be known as the "Lasagna Committee," and is staffed by the National Cancer Institute.

In September, 1989, the Lasagna Committee issued a statement responding to the proposed HCFA coverage rule. The committee concluded that there was essentially no difference between Treatment IND drugs and Group C investigational drugs. The Committee recommended that "Medicare coverage should be identical for all investigational drugs for which safety and efficacy have been demonstrated to a sufficient extent to achieve such treatment use while still in investigational status."[129] It also proposed that HCFA rely upon the authoritative medical compendia[130] in covering drugs prescribed for unlabeled indications. In situations where the compendia are not yet up-to-date on new indications, the Committee recommended creating a panel of experts to assist HCFA in making coverage decisions. Finally, the Committee recommended that Medicare cover associated medical care costs for patients involved in cancer and AIDS trials.

National Cancer Institute: The National Cancer Institute presented its own views on Medicare coverage policy to the Lasagna Committee in January, 1989. The Director of the

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[127]Letter to Dr. Armand Hammer, from George Bush, June 8, 1988.

[128]Proceedings, "National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS," Dr. Armand Hammer, January 4, 1989.

[129]President's Cancer Panel, "Committee Statement Responding to Fed. Reg. Notice of Proposed Rulemaking Regarding Medicare Coverage by the Health Care Financing Administration," National Cancer Program, National Cancer Institute, September 25, 1989.

[130]U.S. Pharmacopoeia, the National Formulary, AMA Drug Evaluations, etc.

Division of Cancer Treatment stated that, "HCFA reimburses expenses for Group C, but not for Treatment IND. There is no rational basis for this distinction. ... Lack of reimbursement discourages doctors as well as patients from utilizing the Treatment IND program to access effective new therapies. Such a situation is clearly contrary to the administration's goal of delivering effective new treatments to the public as expeditiously as possible. The NCI feels strongly that HCFA should reimburse for treatment given under Group C, Treatment IND, or any new combined Group C/Treatment IND category." NCI also indicated that all NCI-sponsored cancer and AIDS trials involving experimental drugs qualify for reimbursement because they represent the best available therapy.[131]

Food and Drug Administration: On March 31, 1989, the Commissioner of FDA commented to HCFA on the Medicare coverage NPRM.[132] FDA indicated that it believes consideration should be given to coverage of Treatment IND drugs because a drug is designated as a Treatment IND drug only when FDA concludes that there is some evidence of effectiveness and reasonable assurance of safety, and that there is no satisfactory alternative therapy. FDA also indicated that Treatment IND drugs represent the best available therapy; the data for approval of the marketing of the drug are being organized by the sponsor or under review by FDA at the time the drug is designated a Treatment IND drug; and Treatment IND drugs are the de facto equivalents to Group C cancer drugs.

Medicaid: In a recent informal survey of a sample of Medicaid Drug Program Administrators, HCFA found that many states do not cover investigational drugs under any

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[131] Comments by Dr. Bruce Chabner, Director of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, January 4, 1989 (Published Transcript).

[132] Letter to Mr. Louis Hays, Acting Administrator, HCFA from Frank E. Young, M.D., Ph.D., March 31, 1989.

circumstances. Several of the states surveyed, however, appear willing to consider coverage for investigational therapies under certain circumstances:[133]

- One state indicated that it determines coverage on a case by case basis.
- One state noted that Treatment IND drugs are currently covered and that the state legislature is considering codifying the coverage.
- One state indicated that investigational drugs may be covered if the drug is a Treatment IND drug, there is a charge for the drug, and the drug is for the treatment of AIDS or an AIDS related condition. In these cases, individual drugs are reviewed for coverage.
- Another state prohibits payment for medical care and services that are investigational or experimental. However, if FDA provides guidelines for the safe administration of an investigational drug, and these guidelines meet the approval of the state Department of Health, the state will consider coverage of the drug. In these cases, a prior approval process would be required for each individual patient.
- In another state surveyed, investigational drugs are generally not covered, but a patient's physician or pharmacist may request authorization for approval of investigational drugs, on a case by case basis.

PRIVATE SECTOR POLICIES

Several associations representing manufacturers and insurers have also addressed the issue of insurance coverage for investigational drugs.

Pharmaceutical Manufacturers Association: In its response to the HCFA coverage NPRM, the Pharmaceutical Manufacturers Association (PMA) noted that, although manufacturers frequently do not charge for Treatment IND drugs, some Medicare contractors are denying medically necessary care associated with administration of Treatment IND drugs.[134] In

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[133]Internal memorandum to David Higbee from Annette Byrne on State Medicaid Policy Regarding Coverage of Investigational Drugs, February 16, 1990.

[134] Letter to Mr. Louis B. Hays, Acting Administrator, HCFA from Robert F. Allnutt, Executive Vice President of Pharmaceutical Manufacturers Association, March 31, 1989.

addition, in response to a report by the Institute of Medicine on Resources for Clinical Investigation[135], the PMA indicated that incremental costs attributable to the evaluation of investigational drugs should be borne by the drug sponsor, while standard costs attributable to patient treatment should be borne by third-party payors.

Health Insurance Association of America: In May 1989, the Health Insurance Association of America (HIAA), which represents some 320 commercial insurance companies, established a task force to review coverage issues associated with off-label use of approved drugs, Treatment IND drugs, Group C cancer drugs, and orphan drugs. The purpose of the task force was to develop a framework for insurers to address coverage of unapproved drugs.[136] The resulting framework is intended to provide guidance to insurers, who are responsible for making their own coverage decisions.

Prior to development of the framework, HIAA conducted an informal survey to better define current policies among health insurance companies. HIAA found that insurers cover services which are "reasonably necessary" in the treatment of an accidental bodily injury or diagnosed illness.[137] "Reasonably necessary" includes items that are (1) ordered by a physician; and (2) commonly and customarily recognized by the physician and medical profession as appropriate. Other insurers use the term to include services "considered by

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[135]In 1988, the Institute of Medicine issued a report on Resources for Clinical Investigation. The report recommended: "There are diseases for which appropriate and required care involves investigational protocols. Such diseases include certain types of cancer, genetic diseases, and possibly other severe, life-threatening diseases. In these cases, third-party payers (government and non-government) should pay the standard patient care costs while costs related to the investigational conclusions should be borne by the sponsoring agency." Report of a Study by a Committee of the Institute of Medicine, Division of Health Sciences Policy. National Academy Press, Washington, D.C. 1988.

[136]Statement of the Health Insurance Association of America, before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, October 25, 1989.

[137]Id.

a majority of the medical profession to be necessary, appropriate and non-experimental; and considered not in conflict with accepted medical standards."[138]

HIAA has developed the following voluntary, non-binding guidelines to assist insurers in assessing emerging and new technologies:[139]

> **Investigational New Drugs**: For immediately life-threatening conditions, Treatment IND drugs, and Group C drugs, each drug should be evaluated to determine its demonstrated benefit.
>
> **Off-Label Use for serious or non-life threatening conditions**: Initially, insurers should consider using drug compendia as reference sources for the off-label uses of drugs. Insurers should review the literature to determine if there are sufficient data to establish safety and effectiveness. Insurers may also consult appropriate medical specialty organizations. And insurers should consider consulting other sources of information, such as experts in the field or researchers.
>
> **Off-Label Use for Immediately Life-threatening Conditions:** Off-label use should not be considered ineligible for coverage on the basis of being experimental. Insurers should assess the results from clinical trials and consult with knowledgeable practitioners. If no other reasonable alternative therapy exists, insurers should be flexible in considering coverage.

HIAA offers the following recommendations regarding payment for investigational drugs:[140]

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[138] Id.

[139] Id.

[140] Id.

- An effective mechanism should be established to review evidence supporting the appropriate use and coverage of unapproved drugs. This could be done by FDA or through a new or existing entity of expert clinicians who would inform providers and payers about currently accepted drug therapies.

- FDA should be encouraged to continue expediting the approval process for treatment INDs for life-threatening conditions, without compromising standards for safety and efficacy.

Blue Cross and Blue Shield Association: On October 25, 1989, the Blue Cross and Blue Shield Association (BCBSA) presented its policies regarding investigational and off-label drug coverage to the Lasagna Committee.[141] The BCBSA is the national coordinating agency for the 73 Blue Cross and Blue Shield Plans. Each Plan provides insurance benefits to its subscribers in accordance with locally drafted contract language and coverage policies. The Association provides support services to the Plans, including technology assessment and coverage information. All information on coverage which the Association provides to the Plans is advisory and informational. Plans make their own coverage determinations.[142]

The guiding principle of the BCBSA is to provide access to effective treatment. The BCBSA recommends that investigational technologies not be eligible for coverage because insurance coverage is limited to treatments that are known to be effective. This principal is implemented by paying for services that are medically necessary; by not covering investigational treatments; and by covering services which have appropriate regulatory approval.[143],[144]

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[141]Presentation by David Tennenbaum, Blue Cross and Blue Shield Association, before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, October 25, 1989.

[142]Id.

[143]Id.

[144] The BCBSA does not mean to imply that Group C or Treatment IND drugs are ineffective. The issue, rather, is what constitutes sufficient evidence of efficacy. BCBSA has relied on FDA approval for marketing as the standard for demonstrating efficacy for drugs.

The Association's Technology Evaluation and Coverage Program evaluates new medical technologies. To be considered eligible for coverage, the scientific evidence must permit conclusions that the use of a technology improves health outcomes such as length of life and ability to function.[145]

The Association made the following recommendations regarding coverage for Treatment INDs and off-label drug use.[146] These recommendations are strictly advisory to the Plans. Each independent Plan determines its own coverage policy.

> **Treatment INDs and Group C drugs**: Treatment INDs and Group C drugs are considered to be investigational because their efficacy has not been established sufficiently to warrant full FDA approval for marketing. The Association believes that coverage of Treatment INDs and Group C drugs would be inconsistent with the principle of coverage for effective treatment.
>
> However, local Plans have shown flexibility and responsiveness in addressing the needs of subscribers with AIDS, cancer and other desperate illnesses. Plans have developed case management and innovative programs to be responsive to the needs of seriously ill patients. For example, many Plans covered AZT and aerosolized pentamidine while these drugs were designated as Treatment INDs.
>
> **Off-Label**: The Association has indicated that the lack of specific FDA approval for a particular indication does not mean that such use is unsafe or ineffective. Off-label indications should not be automatically excluded from coverage consideration, but should be evaluated to determine if their use improves health outcome. Plans should refer to the major drug compendia

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[145] Id.

[146] Id.

as one set of resources when considering coverage of off-label drug uses. Clinical literature and expert opinion should also be considered.

BCBSA also expressed concern about the parameters for Treatment IND designation. It considers this category to be a "moving target" because drugs may be receiving designation increasingly early in the development process, and farther from the point of marketing approval. BCBSA also indicated that all promising interventions for the desperately ill need to be addressed, including drugs, treatments, procedures and devices.[147]

[147] Id.

CHAPTER FIVE:
ANALYSIS AND OPTIONS

This chapter presents an analysis of the issues raised in the previous chapters regarding the relationship between FDA's release of investigational drugs for treatment purposes and the HCFA coverage criteria. The chapter lays out options for the possibility of covering investigational drugs under Medicare and explores the economic implications of coverage.

DISCUSSION

In recent years FDA has accelerated the review process for drugs and biologicals for serious and life-threatening diseases and has permitted investigational drugs to be made available for treatment prior to approval for marketing. At the same time, the Health Care Financing Administration (HCFA) has proposed in regulation its criteria and procedures specifying health care technologies that could be considered "reasonable and necessary" and therefore covered under Medicare.

While the FDA has taken steps to make drugs more widely available prior to approval for marketing, HCFA indicated in its January 1989 NPRM that it will only cover items and services (with the exception of Group C cancer drugs) which have been proven safe and effective based on authoritative evidence, or that are generally accepted in the medical community as safe and effective for the condition for which they are used.[148] Medicare does not cover drugs that FDA has permitted to be made available for treatment purposes but are still considered experimental. Because of this apparent discrepancy between FDA and HCFA policies, certain patients and providers, particularly those dealing with cancer and AIDS, are demanding a change to the HCFA coverage policy for investigational drugs.

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[148]54 Fed. Reg. 4317 (January 30, 1989).

Those Medicare eligible persons who are seeking access to investigational drugs are likely to be seriously ill, so the cost of their care would typically be covered under current Medicare coverage policies, particularly on an inpatient basis. Under the Prospective Payment System (PPS), payment is made for diagnosis related groups (DRGs).[149] No amount is deleted from the hospital's payment when an experimental drug is used.

Still, the issue of Medicare coverage of investigational drugs is somewhat confusing. Many of these drugs are administered on an outpatient basis and are therefore generally not covered under Medicare, even if approved by FDA. However, the majority of chemotherapeutic agents for cancer therapy are administered pursuant to a physician's services (i.e., intravenously in the physician's office) and are therefore covered under Medicare.

There is also legitimate concern over the appropriateness of insurance coverage for therapies that are not proven safe and effective. While it may be appropriate to make drugs available for seriously ill persons before extensive safety and effectiveness data have become available, it does not necessarily follow that insurers should be responsible for paying for unproven therapies. In addition, while the cost of these drugs is currently borne by drug sponsors as part of the cost of research, any significant modification in coverage policy could potentially cause a shift in responsibility for paying for some aspects of research from manufacturers to insurers. This potential shift could have major policy and economic ramifications.

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[149]The Social Security Amendments of 1983 required that a hospital be paid at a predetermined, specific rate for each Medicare discharge based on one of the different DRGs that have been established. The formula used to calculate payment for a specific case takes a hospital's payment rate per case and multiplies it by the weight of the DRG to which the case is assigned. Each DRG weight represents the average resources required to care for cases in that particular DRG relative to the national average of resources consumed per case by the average hospital. Each Medicare discharge is assigned to only one DRG regardless of the number of services furnished or the number of days of care provided. 1988 Medicare Explained, Commerce Clearing House, Inc.

Nonetheless, the issue of Medicare coverage for investigational drugs remains highly visible because of the growing perception that coverage is being denied to those for whom investigational drugs may be the best available therapy. There is concern that insurance will determine who gets what therapy and that only those patients with adequate financial resources will obtain the most innovative treatment. Pressure is mounting on HCFA because it is viewed as the trend-setter in coverage policy; any change in HCFA coverage policy could serve as a precedent for Medicaid and private insurance coverage for investigational drugs.

OPTIONS

The following is a series of options for the possibility of coverage of investigational drugs. The options range from maintaining current Medicare coverage policy, to expanding coverage to include all Treatment IND drugs; or in the alternative, to include selected investigational drugs, either on a drug-by-drug basis as a national coverage policy, or on a patient-by-patient basis at the discretion of local contractors. A fifth option is to eliminate coverage for Group C drugs. Each option has relative strengths and weaknesses, and each could have some economic impact on Medicare.[150]

Option One: Maintain the current Medicare drug coverage policy

The current Medicare policy does not cover investigational drugs, with the exception of Group C cancer drugs. This option is consistent with the rationale provided by HCFA in its January 1989 coverage regulation, which indicates that the use of investigational drugs is considered research, and that there are insufficient safety and effectiveness data for such drugs to warrant coverage. From HCFA's viewpoint, since there is no significant evidence that care is being denied to the Medicare population under the current policy, there appears

[150]In this discussion of the options, the economic impact of drug coverage is presented within the context of current Medicare benefits. Since the majority of individuals using investigational drugs are seriously ill, it is assumed that their inpatient care is covered currently. For investigational drugs used on an outpatient basis, it is assumed that current limitations on coverage would be maintained.

to be little rationale for expanding coverage to include investigational drugs. And since drugs available for treatment use prior to marketing approval are still investigational, it is not apparent that these drugs are actually safe and effective enough for Medicare's purposes. HCFA also argues that Medicare should not bear the cost for and encourage the use of Treatment IND drugs through insurance coverage. HCFA believes that Treatment IND drugs can be at different stages of development and may have inadequate safety and effectiveness evidence to warrant coverage, while Group C cancer drugs do have adequate evidence of safety and effectiveness. HCFA has also indicated that it is trying to rely more heavily on assessing the effectiveness of medical care, and that coverage of Treatment IND drugs would be inconsistent with this approach. And, finally, HCFA believes that if coverage were expanded to include investigational drugs, then a "slippery slope" of coverage for investigational devices and procedures would follow.

However, by maintaining the current policy Medicare will continue to face opposition from those who argue that beneficiaries are being denied coverage for appropriate care. These groups argue that HCFA's coverage policy should be consistent with FDA's policy of designating certain drugs for treatment use before they are approved for marketing. These groups also argue that HCFA should treat investigational drugs comparably with breakthrough medical procedures for seriously ill patients where coverage may be allowed for breakthrough medical or surgical procedures if no safer or more effective treatments are available, and that HCFA should play a leadership role with regard to coverage.

Option Two: Expand coverage to include Treatment IND drugs.

Under this option, Medicare would continue to rely on FDA's expertise in making its coverage decisions for drugs. However, instead of linking coverage to FDA approval for marketing, HCFA could adopt as its standard a more general reliance on FDA's regulatory decisions, including a determination by FDA that a drug may be designated for treatment use (e.g., Treatment IND). FDA has indicated that Treatment IND drugs should be covered under Medicare because: (1) there is some evidence that Treatment INDs are safe and effective, (2) there is no satisfactory alternative therapy, (3) the Treatment IND drug is the

best available therapy, (4) the Treatment IND drug will likely be approved for marketing once the clinical studies are complete and the data have been reviewed by FDA, and (5) Treatment IND drugs are equivalent to Group Cs, which are already covered.[151]

Under this option, HCFA would not cover all investigational drugs, since it is apparent that not all investigational drugs are comparable. FDA has clearly indicated in regulations that Treatment IND drugs are a formal, intermediate category between clinical investigation and marketing approval. Therefore, Medicare could defer to the FDA designation for Treatment IND drugs and could continue to apply its established coverage criteria, i.e., (1) general acceptance in the medical community; and (2) furnished in the appropriate setting by qualified personnel, in combination with its criteria for coverage of Group C cancer drugs and breakthrough medical or surgical procedures for persons who are seriously ill.

This option would be responsive to concerns that HCFA policy is inconsistent since it covers Group C drugs but not Treatment IND drugs. Medicare could conclude that since both these categories of investigational drugs are designated by FDA for treatment uses, such drugs constitute the best available treatment for use in certain patients and are "reasonable and necessary" for them. On the other hand, HCFA could continue to argue that any investigational drug not approved for marketing (other than Group C cancer drugs) is investigational, and therefore not safe and effective. HCFA could also argue, as noted in Option 1, that coverage of Treatment IND drugs could lead to demands for coverage of investigational devices and procedures. However, FDA has not created a comparable category of "Treatment" investigational devices as it has for drugs, and there is no regulatory designation for procedures.

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[151] Letter to Mr. Louis Hays, Acting Administrator, HCFA from Frank E. Young, Commissioner, FDA, March 31, 1989.

This option would not represent a large net cost to the Medicare program since most Treatment IND drugs are provided without charge, and many of the drugs are provided on an outpatient basis, which is not a covered service under Medicare. For patients who receive these drugs on an inpatient basis, there would probably be no additional charges under the current hospital payment system.

Option Three: Expand coverage to include selected investigational drugs, on a drug-by-drug basis.

Another approach that could be considered is a drug-by-drug national coverage policy. This would represent a national, uniform Medicare coverage policy for selected investigational drugs. HCFA would review specific drugs approved by FDA for treatment distribution, using its own coverage criteria to determine the appropriateness of coverage for individual drugs, based on the level of evidence available. Medicare could cover some, but not all Treatment IND drugs, Group C drugs, and perhaps other INDs, based on evidence of safety and effectiveness. Under this option, Medicare could even delay coverage of selected investigational drugs released by FDA for treatment distribution until additional data had been reported on use in a widespread population, but would cover these drugs prior to their obtaining marketing approval. The advantage of this option is that it provides HCFA with the most discretion to distinguish among investigational drugs that may be available for treatment.

However, HCFA does not currently have the expertise to make drug-by-drug assessments, particularly for drugs that are still investigational. Therefore, HCFA would have to develop a mechanism to determine which individual drugs would be covered. This could be done under the existing technology assessment process[152], although the current process is often lengthy. Another approach would be for HCFA to rely on FDA to provide an indication

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[152]See 54 Fed. Reg. 4305 (January 30, 1989). Note, however, that even with regard to devices, HCFA's independent reviews are a rarity, often lengthy, and undertaken on an exceptions basis, primarily by referral to PHS for preliminary analysis. Typically, HCFA requests less than twenty-five assessments per year, and PHS requires months to respond. Thus, implementation of this approach for drugs should be understood to require both significant new resources and substantial amounts of time.

of the amount of safety and effectiveness information available for individual drugs based on the completion of clinical trials. Under this option Medicare could reserve the right to withdraw coverage of individual drugs if serious adverse effects or other problems arose after the drug was distributed.

One potential problem with this approach is that the information on effectiveness necessary for coverage determination might not be readily available to HCFA because it is not published. FDA receives safety and efficacy data submitted as part of new drug applications, but FDA cannot release these data because they are protected as confidential commercial information. Still another approach would be to contract with an outside group of experts as suggested by the Lasagna Committee,[153] although such a group would also be unable to get the data from manufacturers necessary for coverage determinations.

All of these approaches could be cumbersome, with limited real value to Medicare beneficiaries since most outpatient drugs are not covered and drugs used on an inpatient basis are probably covered under the current hospital DRG payment system. Also, this approach could continue to put Medicare in a position of not covering some drugs designated by FDA for treatment use, while covering other drugs.

This option would not represent a large net cost to the Medicare program since most Treatment IND drugs are provided without charge, and many of the drugs are provided on an outpatient basis, which is not a covered service under Medicare. For patients who receive these drugs on an inpatient basis, there would probably be no additional charges under the current hospital payment system. It would cost less than option 2 above because not all Treatment IND drugs would necessarily be covered.

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[153]President's Cancer Panel, September 25, 1989.

Option Four: Permit contractors to consider coverage for investigational drugs on a patient-by-patient basis.

This option is consistent with the Medicare policy for off-label use of drugs[154] and the recent HIAA policy statement[155] regarding investigational drug coverage. Under this option, individual contractors would be given explicit authority to review the use of investigational drugs on an individual patient basis. Local providers and their patients could potentially have a greater ability to obtain coverage for certain investigational therapies, on a patient-by-patient basis, than under current Medicare rules.

However, the implementation of this option would exacerbate problems currently associated with the discretion of local contractors, where patients in one region might have better access to coverage for investigational therapies than patients in another region. Moreover, the question arises whether contractors have the resources or expertise to evaluate investigational drugs. This problem would also apply to Medicare risk contractors (HMOs) who make their own coverage decisions. Unlike off-label use, where the contractor can turn to the published literature or to the provider community for guidance, investigational drugs by definition are not widely utilized among providers, and therefore are not adequately discussed in peer-reviewed published literature.

The economic implications of this option would likely be negligible for the reasons discussed in options 2 and 3 above. However, the variations in coverage by contractors could lead to an uneven impact in different regions.

Option Five: Eliminate coverage for Group C cancer drugs

Under this option, Medicare would cover only drugs that FDA has approved for marketing pursuant to the NDA process, thereby eliminating coverage for Group C cancer drugs. This option has the advantage of ensuring consistency in Medicare's treatment of drugs not

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[154]54 Fed. Reg. 4306 (January 30, 1989).

[155]Statement of the Health Insurance Association of America, October 25, 1989.

approved for marketing by FDA. Moreover, it is not completely evident that Group C drugs always have adequate safety and effectiveness data for marketing approval, or that they are significantly different from Treatment IND drugs, which are not currently covered under Medicare.

However, the FDA, NCI, providers and cancer patients would view implementation of this option as a major retraction of coverage, and would likely oppose any such policy. Eliminating coverage for Group C drugs would provide virtually no savings to Medicare since the drugs are provided at no charge and are often administered on an outpatient basis, which is not a covered benefit. However, if the care associated with the use of these drugs were denied, then Medicare would reduce expenditures. The negative perception associated with this option would far outweigh any economic effect.

ECONOMIC IMPACT OF EXPANDED MEDICARE COVERAGE

None of the options discussed above would create significant short-term costs to the Medicare program. To date, most Treatment IND drugs and Group C drugs have been provided to patients at no charge. In addition, because the majority of patients using these drugs have serious and life-threatening illnesses, the cost of their care is already covered as part of current benefits.

However, there could be short and long-term economic implications if drug companies began to charge for the use of investigational drugs and if coverage for Treatment IND drugs resulted in payment for any incremental hospital and physician care that had previously been provided as part of a research protocol.

To date, only three of seventeen Treatment IND drug sponsors have charged for their product, but this could change if Medicare covered these drugs under the current benefit system. However, the research community and the PMA have indicated that drug sponsors should bear the costs of investigation for their products. If companies began to charge and

if additional costs were incurred for associated hospital and physician care, and a larger number of Medicare beneficiaries began to use such investigational drugs, then there could be a significant net increase in Medicare expenditures.

In addition, coverage of investigational drugs could serve as a precedent for coverage of investigational devices and procedures, which could have a far larger impact on Medicare expenditures.

Any economic projection about the impact of expanded coverage is dependent upon a number of variables, including: (1) the range of serious and life-threatening diseases that might be appropriate for early access to investigational therapies; (2) the number of Medicare beneficiaries with these serious and life-threatening diseases; (3) the number of investigational drugs that would be available for treatment; (4) the cost of these investigational drugs; (5) the incremental cost of care associated with use of the drugs; (6) the demand for these drugs by Medicare beneficiaries; and (7) the induced supply and demand for these drugs potentially created by expanded coverage.

1. **Serious and Life-Threatening Diseases**: Figure 5.1 shows the list of serious and life-threatening diseases included in the FDA Treatment IND regulations. Many of these diseases disproportionately affect the Medicare population.

2. **Number of Medicare Beneficiaries**: As noted in Chapter Three, Medicare beneficiaries are Social Security beneficiaries who are eligible to receive a health care benefit through the Medicare program. They include almost all persons 65 and older, persons under age 65 who have been disabled for two or more years, and persons of any

FIGURE 5.1

Life-threatening and Serious Illnesses

LIFE THREATENING

AIDS
Advanced cancer
Bacterial endocarditis
Congestive heart failure
Far-advanced emphysema
Herpes simplex encephalitis
Recurrent, sustained
  ventricular tachycardia and
  ventricular fibrillation
Subarachnoid hemorrhage

SERIOUS

Advanced multiple sclerosis
Advanced Parkinson's
Alzheimer's disease
End-stage renal disease
Nonacidotic diabetic coma
Transient ischemic attacks

Source: 52 Fed.Reg. 1946-7 (May 22, 1987).

age with End-stage Renal Disease (ESRD) who require renal dialysis or a kidney transplant. The number of Medicare beneficiaries in 1988 totaled almost 33 million.

The number of Medicare beneficiaries with serious and life-threatening diseases varies widely by disease. For example, patients with diseases such as Alzheimer's and advanced Parkinson's disease are mostly Medicare beneficiaries, while less than three percent of AIDS patients are currently Medicare beneficiaries. However, with the use of improving therapies, patients with HIV/AIDS may live longer with chronic HIV/AIDS and could become eligible for Medicare through disability or age.

3. **Number of Investigational Drugs Available for Treatment:** As highlighted in Chapter Two, there has been a limited number of drugs made available for treatment use. Based on current experience, therefore, the number of investigational drugs available for treatment is expected to remain relatively small.

4. **Cost of investigational drugs:** With a few exceptions, manufacturers have provided investigational drugs without charge. As noted above, however, expanded coverage could serve as an incentive to manufacturers to charge for Treatment IND drugs.

5. **Cost of Associated Care:** Since persons using Treatment IND drugs are seriously ill, it is likely that much of the cost of their care is already covered under current Medicare benefits. However, the use of investigational drugs may require additional hospital admissions and physician visits and entail additional laboratory tests. In addition, there could be increased cost associated with the treatment of side-effects related to the use of investigational drugs. Group C drugs and their associated care are already covered by Medicare, although the drugs themselves are always provided at no charge.

6. **Demand for investigational drugs:** Because Medicare beneficiaries are elderly or disabled, they are more likely than the general population to have concomitant medical conditions and be ineligible for participation in clinical trials using investigational drugs.

Other patients may not seek investigational drugs because they, or their physicians, lack interest or awareness. It is also unclear whether some Medicare beneficiaries would be as willing to take the risks associated with the use of investigational drugs as would younger patients, although these patients have participated in NCI-sponsored clinical trials because they believe that they offer the best chance for survival.

7. **Induced supply and demand**: It is difficult to project the induced supply and demand that could be created by expanded coverage for investigational drugs. The availability of investigational drugs for widespread treatment has been limited thus far; it is not obvious that a modified HCFA coverage policy would provide a major incentive for manufacturers to make more drugs available during the investigational phase of development or to charge for the types of investigational drugs that had previously been provided at no charge.

It is equally unclear what effect expanded coverage could have on demand for investigational drugs. As noted above, Medicare beneficiaries are elderly or disabled, and may be in generally poor health. Further, this population may be averse to the risk associated with the use of investigational drugs, although they have participated in cancer clinical trials in the past. There is some chance that expanded coverage could induce additional demand for these drugs, but given that the supply is not likely to increase rapidly, that the care associated with serious illness is already covered by Medicare, and that to date, these drugs have been provided at no charge, there is not likely to be a significant short-term increase in Medicare expenditures resulting from any demand induced by expanded coverage. However, as indicated earlier, expanded coverage to include certain investigational drugs could have vast economic implications if coverage were also expanded to include costly investigational devices and procedures.

LONG-TERM COST

If Medicare were to expand coverage to include additional investigational drugs, Medicare costs could increase in the long term for the following reasons:

- The number of persons over age 65 is expected nearly to double by the year 2020, to 50 million. In addition, any change in the number of persons with AIDS or HIV who are eligible for Medicare could result in a substantial increase in the number of patients using investigational drugs under Medicare.

- PHS initiatives such as "parallel tracks" may expand the availability of investigational drugs for treatment use. As manufacturers, providers and patients become more familiar with treatment use of investigational drugs, supply and demand for these products may increase.

- If a drug were made available to treat a common illness among the elderly, such as Alzheimer's or Parkinson's, then a larger number of Medicare beneficiaries might demand access to certain investigational drugs.

- Expanded coverage for investigational drugs could create an incentive for drug manufacturers, who previously provided most Treatment IND drugs at no charge, to begin charging for their products.

While it is possible that these factors could increase Medicare's cost exposure, it is also possible that Medicare's cost exposure will remain the same or decrease in the long term for the following reasons:

- Thus far, a very small number of investigational drugs has been made available outside of clinical trials. There is limited evidence to suggest that sponsors will vastly increase the number of investigational drugs available for treatment, and if any severe adverse effects occur or a sponsor is held liable for any adverse events, the number of investigational drugs made available for treatment prior to marketing approval may actually decrease.

- Providers could be reluctant to consider investigational drugs for patients, particularly for Medicare beneficiaries who are older or disabled and who may be in poor health. Liability concerns may also hamper physician participation.

- It is not apparent that the majority of the Medicare population would be appropriate to receive investigational drugs because of concomitant medical conditions. It is also not clear whether Medicare beneficiaries would be willing to take the risks associated with the use of drugs whose safety and effectiveness are relatively unproven, although historically patients in this age group have participated in NCI-sponsored clinical trials.

- If an investigational drug used for treatment proves a "breakthrough," there could be considerable cost savings due to decreased hospitalization charges, etc. as compared to treatment with less effective therapies.

Finally, there is a potential "slippery slope" of coverage. If Medicare were to cover selected investigational drugs, it could be faced with pressures to cover investigational devices and procedures. Such an expansion of coverage could have a significant impact on Medicare expenditures.

CONCLUSIONS

Based on an analysis of existing regulatory policy, experience to date with the use of investigational drugs for widespread treatment, and a review of the issues associated with insurance coverage for investigational therapies, it appears that:

- Not all investigational drugs are equivalent; rather there is a continuum of development with different drugs having different amounts of data regarding their safety and efficacy.
- Treatment IND drugs represent a specific category of investigational drugs that FDA has designated for potentially widespread treatment use, within the guidelines of the Treatment IND protocol, but outside the clinical trials setting. Treatment IND drugs are a formal intermediate category between clinical investigation and marketing approval. No comparable designation exists for devices or for medical procedures.
- Of all the investigational drug categories designated by FDA, Treatment IND drugs and Group C drugs differ in several significant respects from investigational drugs distributed in clinical trials. Medicare could modify its exclusive reliance for coverage on FDA marketing approval for drugs and defer to FDA's designation of Treatment IND drugs as it does for Group C cancer drugs.

- Expanded coverage by Medicare for selected investigational drugs would likely have limited immediate impact on expenditures, although coverage for investigational drugs could set a precedent for coverage of investigational devices and procedures.

- Other third-party payors appear to be modifying their policies to allow for some coverage of investigational drugs.

Whether or not any changes are made to Medicare and other third- party coverage policies, additional efforts should be made to help clarify and resolve the complex issues of insurance coverage and drug approval:

- FDA should review its policies regarding the use of investigational drugs for treatment purposes. The Agency should clarify the circumstances under which an investigational drug that is not a Treatment IND drug may be made available for treatment use. Such clarification is critical for informing patients, providers, researchers and insurers about the FDA criteria for permitting the treatment use of investigational drugs.

- Medicare should reassess its criteria for "reasonable and necessary" care, particularly for patients with serious and life-threatening conditions and in light of the designation by FDA of Treatment IND drugs. Medicare should consider the rationale for having different safety and effectiveness standards for drugs, devices, and other services at a time when FDA policy on treatment availability of investigational drugs is changing.

- NCI, FDA and HCFA should resolve their different perceptions about Group C cancer drugs. If it is agreed that Group C drugs are equivalent to Treatment IND drugs, then HCFA should consider making consistent its coverage policy, which now distinguishes between these two categories.

- The issue of payment for the components of research and treatment, including associated care, should be further explored among third-party payors, drug sponsors, government, and the business community.

- Patients, providers, drug sponsors, researchers, and regulators must continue discussions on the changing health care delivery system, the role of insurance in paying for appropriate care, and the relationship between access to care and payment for care.

APPENDIX A

GLOSSARY

STUDY ON COVERAGE OF INVESTIGATIONAL DRUGS AND BIOLOGICAL PRODUCTS UNDER THE MEDICARE PROGRAM

Organizational Acronyms

BCBSA -- Blue Cross and Blue Shield Association

FDA -- Food and Drug Administration, U.S. Department of Health and Human Services

DCT -- Division of Cancer Treatment, National Cancer Institute, National Institutes of Health

HCFA -- Health Care Financing Administration, U.S. Department of Health and Human Services

HIAA -- Health Insurance Association of America

HHS -- U.S. Department of Health and Human Services

NCI -- National Cancer Institute, National Institutes of Health

NIH -- National Institutes of Health, U.S. Department of Health and Human Services

PHS -- Public Health Service

PMA -- Pharmaceutical Manufacturers Association

Other Definitions

Biological product -- a virus, serum, toxin, antitoxin, or analogous product (e.g., blood or blood component or derivative or allergenic product) intended for use as a therapeutic.

Carriers -- Medicare contractors who are responsible for the administration of Part B of the Medicare program and for assuring that payments to providers are made only for covered services.

Clinical investigation -- any use of a drug, except for the use of a marketed drug in the course of medical practice, in which a drug is administered to, or dispensed to, one or more human subjects.

Clinical studies -- human studies aimed at distinguishing a drug's effect from other influences.

Compassionate use -- a general term referring to situations in which FDA has permitted a drug that has not been approved for marketing to be distributed to physicians for treatment use. Compassionate use is not intended to provide research data that would support an application to market the drug.

Cost of associated care -- the cost of medical services and supplies that are incurred in the course of receiving investigational drugs, e.g., physician or nurse's time to administer the drug, hospitalization required in order to receive the drug.

Covered services -- drugs, diagnostics, medical supplies and procedures to which Medicare eligibles are entitled as benefits of the Medicare program. Coverage decisions are distinct from reimbursement decisions, which establish the amounts to be paid for covered items.

Coverage criteria -- standards used by HCFA for determining whether a service is "reasonable" and "necessary" and, therefore, covered under the Medicare program.

Coverage decisionmaking -- the process by which HCFA decides whether an item or service is eligible for payment under Medicare.

Drug -- product intended for use in diagnosing, curing, mitigating, treating or preventing disease; products intended to affect the structure or any function of the body; and products recognized in one of three official pharmacopeia and formularies.

Efficacy -- the measure of a drug's influence on a disease or condition. In order for a drug to be approved for marketing, federal law requires substantial evidence of effectiveness consisting of adequate and well-controlled investigations that prove the drug will have the effect claimed in its labeling.

Experimental -- see Investigational.

FDA-approved -- the approval of a drug or biological product by the Food and Drug Administration for general marketing.

Group C drugs -- investigational anticancer drugs that are sponsored by the NCI and made available for treatment use. Unlike other drugs distributed by the NCI, Group C drugs are not limited to use in clinical trials. Their distribution for treatment use is subject to FDA approval.

Institutional review board (IRB) -- boards composed of scientific, medical and lay persons who are responsible for monitoring research involving human subjects within their institutions.

Investigational -- a term used to describe the degree to which a new health care technology has been developed and accepted within the medical community. Probably the most common use of the term is to describe drugs or devices that have not yet been approved for marketing by the FDA.

Investigational new drug -- a new drug, antibiotic drug or biological drug that is used in a clinical investigation.

Investigational New Drug Application (IND) -- an application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study.

Life-threatening -- diseases and conditions where the likelihood of death is high unless the course of the disease is interrupted, as well as diseases or conditions with potentially fatal outcomes.

Medicare -- a federally-funded health insurance program that provides payment for certain medical services and supplies to persons 65 years of age or over, disabled beneficiaries, and persons with end-stage renal disease.

Modified Group C drugs -- a subset of Group C drugs distinguished by the extraordinary level of medical support and scientific expertise required for their safe administration.

New drug application (NDA) -- a submission by the sponsor to the FDA for approval to market a new drug for human use. Among other information provided, the NDA must demonstrate the safety and efficacy of the drug.

Open Protocols/Open Label studies -- one type of distribution of investigational drugs to patients not participating in clinical studies. FDA permits such distributions for the dual purpose of providing treatment and collecting safety data. This distribution typically involves hundreds or even thousands of patients.

Outpatient drugs -- prescription drugs administered to patients who are not hospitalized or otherwise institutionalized, e.g., at home, in a physician's office, in the outpatient department of hospital.

Off-label use -- non-labeled uses or off-label uses may be defined as the use of certain prescription drugs for conditions not named in the official labeling.

Product License Application (PLA) -- a submission by the sponsor to FDA for approval to market a biological product for human use. Among other information provided, the PLA must have evidence showing safety, efficacy, purity and potency.

Supplementary Medical Insurance Program (Medicare Part B) -- one of two complementary insurance programs under Medicare that pays for a wide range of medical services and supplies, such as physician services, outpatient hospital services, outpatient physical therapy, rural health clinic services, durable medical equipment and certain drug and biological products.

Treatment use -- use of investigational drugs or biological products to treat patients outside of clinical trials.

APPENDIX B

ADVISORY BOARD MEMBERSHIP

STUDY ON COVERAGE OF INVESTIGATIONAL DRUGS AND BIOLOGICAL PRODUCTS UNDER THE MEDICARE PROGRAM

Dr. Karen Antman
American Society of Clinical Oncologists,
Public Issues Committee
Dana-Farber Cancer Institute
Boston, Massachusetts

Mr. Gary Claxton
Senior Analyst,
Public Policy Institute
American Association of Retired Persons
Washington, D.C.

Dr. Julius Cruse
Department of Pathology
University of Mississippi Medical Center
Jackson, Mississippi

Dr. Robert Enck
Home Health Care Advisory Group
American Medical Association

Dr. Leonard Fenninger
Physicians Association for AIDS Care
Northwestern University

Ms. Susan Gleeson
Director
Technology Management Department
Blue Cross/Blue Shield Association
Chicago, Illinois

Mr. Joel Miller
Insurance, Managed Care and Provider
Relations Division
Health Insurance Association of America
Washington, D.C.

Ms. Susan Jelley Palsbo
Senior Research Associate
Group Health Association of America
Washington, D.C.

Dr. Marian Parrott
American College of Physicians
George Washington University
Medical School
Suite 5429
Washington, D.C.

Dr. John Petricciani
Vice President, Medical and Regulatory
Affairs
Pharmaceutical Manufacturers Association
Washington, D.C.

APPENDIX C

INTRADEPARTMENTAL WORKGROUP MEMBERSHIP

STUDY ON COVERAGE OF INVESTIGATIONAL DRUGS AND BIOLOGICAL PRODUCTS UNDER THE MEDICARE PROGRAM

Anna Boyd
Policy Coordinator
Executive Secretariat, Office of the
Secretary
Department of Health and Human Services
Washington, D.C.

Annette Byrne
Bureau of Policy Development, HCFA
Baltimore, Maryland

Linda Carter
Office of Drug Evaluation I
Food and Drug Administration
Rockville, Maryland

Allen Duncan
Deputy Associate Commissioner for
Health Affairs
Food and Drug Administration
Rockville, Maryland

Dr. Elaine Esber
Food and Drug Administration
Bethesda, Maryland

Dr. John Ferguson
Director, Office of Medical
Applications and Research
National Institutes of Health
Bethesda, Maryland

Dr. Michael Friedman
Acting Associate Director, Cancer
Therapy Evaluation Program
National Cancer Institute

National Institutes of Health
Rockville, Maryland

Dr. Donald Goldstone
Director, Division of Intramural Research
Agency for Health Care Policy Research
Rockville, Maryland

Dr. Tom Holohan
Office of Health Technology Assessment
Rockville, Maryland

Anne Marie Hummel
Bureau of Policy Development, HCFA
Baltimore, Maryland

Dr. Jack Killen
Deputy Director, AIDS Program
National Institute of Allergy
and Infectious Disease
National Institutes of Health
Rockville, Maryland

Carol Kimbrough
Food and Drug Administration
Rockville, Maryland

Dr. Joyce O'Shaughnessy
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Lee Ripper
Food and Drug Administration
Rockville, Maryland

Iris Schneider
Assistant Director for Program
Operations and Planning
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Ms. Ann Scott

Analyst
Office of Legislation and Policy
Health Care Financing Administration
Washington, D.C.

Ms. Caroline Taplin
Program Analyst
Office of Health Planning
and Evaluation
Public Health Service
Washington, D.C.

Robert E. Wren
Director, Office of Coverage Policy
Bureau of Policy Development, HCFA
Baltimore, Maryland

APPENDIX D
AGENCY COMMENTS

Medicare Coverage for Medical Care of Cancer Patients Receiving Investigational Therapies: An NCI Statement

In the three decades during which our country has built the productive and highly-coordinated cancer clinical trials network in place today, federal and private third-party payors have underwritten the non-research, patient care costs associated with administering investigational therapies. In the past several years, however, with the continued rapid increases in the costs of providing medical care, insurers have become increasingly reluctant to pay for cancer care administered in a clinical trials setting.

This report, "Medicare Coverage for Investigational Drugs: Exploring the Options", includes discussion of the question: Are investigational cancer therapies and cancer clinical trials primarily research or are they primarily treatment? The underlying thesis in the report is that investigational therapies that are primarily for treatment purposes could be considered for reimbursement by the Health Care Financing Administration (HCFA), whereas those that are primarily for research purposes are too premature to consider for such. The National Cancer Institute (NCI) believes that all NCI-sponsored cancer clinical trials are both, research and treatment, and should have reimbursable clinical care costs.

NCI's mission is to generate new knowledge about cancer, and clinical trials are a vital part of this research effort. NCI's appropriation includes funds for research costs of clinical trials, but not for patient care costs. Denial of coverage for these patient care costs will have the effect of closing access to clinical trials and investigational agents for the less affluent members of our society. NCI-sponsored clinical trials generate important new knowledge about investigational drugs or about approved drugs and are therefore appropriately termed clinical investigation. However, all NCI-sponsored clinical trials are designed to offer each cancer patient therapy that is at least equivalent, and the hope is, better, than the current standard care. NCI believes that NCI-sponsored clinical trials represent state-of-the-art treatment for cancer patients. NCI-sponsored clinical trials undergo extensive peer review at multiple levels within the investigator's own institution, in many cases within the NCI-funded Clinical Cooperative Group network, and then at NCI and the Food and Drug Administration (FDA).

It is important to be clear that ethical considerations dictate that the best possible medical care of patients be held primary in the clinical trials setting. From the viewpoints of cancer patients and their physicians, participation in an NCI-sponsored clinical trial is offered with the understanding that the patient's cancer will be treated with state-of-the-art therapy that has a chance of achieving what standard therapy cannot. For patients and

the physicians responsible for their care, therefore, it is the treatment aspects of clinical trials that are paramount.

This treatment versus research issue can cloud the discussion of third-party payment for standard medical care costs for patients participating in NCI-sponsored clinical trials. Perhaps better is to focus on differentiating between ineffective and state-of-the-art cancer care. Third-party payors should not be in the position of paying for ineffective cancer therapies; to some the term research connotes a "shot in the dark" approach where little is known about safety or efficacy. Insurers should, however, reimburse for therapies, approved or investigational (within the context of an NCI-sponsored clinical trial), that have been identified by national experts as state-of-the-art treatment for cancer patients. It is important to realize that many approved and marketed cancer drugs offer a particular cancer patient less of a chance for clinical benefit than does receiving an investigational therapy in an NCI-sponsored clinical trial. NCI suggests, therefore, that issues of reimbursement coverage should not revolve around the terms <u>approved</u> versus <u>investigational</u>, <u>research</u> versus <u>treatment</u>, but rather, around identifying which therapies offer patients the best chance of clinical benefit. NCI believes that NCI-sponsored clinical trials offer this to patients.

Our country has targeted the goal of developing practice guidelines based on yet to be defined standards of effectiveness. In the process, it is hoped, ineffective therapies will be identified, giving third party payors a rational basis for denying unnecessary coverage. Our country has built a highly productive cancer clinical trials network which has established the efficacy of many cancer therapies and has continued to improve the standard of care; this resource is in danger of eroding without continued payment by insurers of the routine medical costs associated with administering investigational therapies. As practice guidelines in cancer are established over the next years, NCI recommends that NCI-sponsored clinical trials which offer state-of-the-art therapy to cancer patients be included in the guidelines and receive third-party coverage. NCI believes that this approach would well serve the interests of cancer patients as well as our country's National Cancer Program.

MEDICARE COVERAGE FOR INVESTIGATIONAL DRUGS COMMENTS BY THE AGENCY FOR HEALTH CARE POLICY AND RESEARCH

The report, Medicare Coverage for Investigational Drugs: Exploring the Options raises but does not address several critical policy issues associated with reimbursement for drugs where questions of safety and effectiveness still remain. These issues make the question of reimbursement in these circumstances far more complex a matter than this report would suggest.

CONTROLLING THE BENEFIT

Drugs represent one form of technological intervention for diagnosing and treating disease; various procedures and devices represent other forms of intervention. To the extent one provides reimbursement for investigational drugs, there is no logical basis for not treating investigational devices and procedures in the same manner. The report describes this as the "... 'slippery slope' of coverage," (Page 73.) However, the matter is treated and dismissed in a sentence. The report provides no sense of the magnitude of the problem.

Under the FDA rules a Treatment Investigational New Drug Application (IND) designation may be provided when a life threatening disease is involved, no alternative effective therapy is available, and there is at least some evidence the experimental therapy might be effective. Similar criteria could be advanced to support reimbursement for a host of yet unproven interventions such as autologous bone marrow transplantation in metastatic solid tumors, hyperthermia for solid tumors, or the use of artificial hearts. A surgeon at Loma Linda University implanted a baboon heart in a human infant based on similar rationale. Similar reasoning was employed as the basis for extracranial/intracranial bypass surgery to treat vascular obstructions and the procedure was not abandoned even after a clinical trial revealed it was not effective. The principal investigators in that trial responding to such arguments stated:

> It is difficult to rationalize the use of a therapy that has not been proven to have any benefit simply because the disease failed to respond to treatment that has known benefit but is not a panacea.

It is difficult to believe that a decision to reimburse for drugs still viewed as experimental will not be followed by a demand to extend the approach to devices and procedures. In estimating the cost of this initiative, this possibility should be taken into account.

SUBSIDIZING RESEARCH

The draft report states, "The issue of payment for research should be further explored among third party payors, drug sponsors, NIH, and FDA." A decision to reimburse for experimental drugs, devices, or procedures would have the effect of subsidizing expenditures now covered all or in part by funds allocated specifically for research purposes.

The question of how we should distribute the costs of research and other forms of investment has not been resolved. Medicare, for example, had until recent years covered the costs of training new physicians working in the hospital setting. Reimbursement for training under the Medicare program has now been severely curtailed on the presumption that Medicare is intended to cover patient costs. The way Medicare now deals with experimental drugs, devices, and procedures is consistent with this approach to training costs. It also has been the case in some States that insurance firms are precluded from applying resources acquired for one purpose through premiums to other use, such as research, no matter how meritorious the activity might be. Any demand that insurers cover research costs would be inconsistent with this policy.

The Federal Government through its appropriation process makes explicit decisions about the proportion of available resources that will be spent on research. To the extent that research costs would be treated and recorded as if they are reimbursement for medical care the ability of the government to set priorities and control the distribution of resources would be compromised. If the government were to conclude that additional expenditures for research to test the value of new technological innovations is appropriate, funds should be explicitly allocated for that purpose.

COMPROMISING RESEARCH OR TREATMENT

One of the problems that should receive more attention than is evident in the report is the degree to which having experimental drugs available for treatment will contaminate the trials designed to test their safety and efficacy. If it is suggested to all individuals with a life threatening disease and no effective alternative therapy available that some sort of new treatment might make a difference, who will reject the opportunity to test the benefit? Under these circumstances how does one establish a control population? Even if some individuals, for whatever reason, agree not to avail themselves of the treatment and provide a pool from which one could draw a control sample, the question of bias would be a matter of concern.

On the other hand, if drugs or devices and procedures are not clearly safe and effective, what justification really exists for their use. It is possible that patients using these questionable

technological advances will be worse off for the experience. For example, a drug might produce mild or serious morbidity or even death without providing any benefits in return. Alternatively, the use of a new drug of still questionable safety and effectiveness with the expectation that some improvement might result could interfere with the use of other palliative therapies. There are many instances where seemingly promising drugs, procedures, or devices have been found in the long run not only to be without benefit but to be harmful instead.